Ex Libris

Oskar Klotz

P
Med
M

UNIVERSITY OF MICHIGAN, Pathological Laboratory

CONTRIBUTIONS

FROM THE

PATHOLOGICAL LABORATORY

ALDRED SCOTT WARTHIN, Ph.D., M.D., Director

UNIVERSITY OF TORONTO LIBRARY

REPRINTS
VOLUME VII
1915–1916

448734
1-7-46

ANN ARBOR, MICHIGAN
1916

CONTENTS

1. Warthin, Aldred S. The Occurrence of Malignant Neoplasms in the Young.
   (From *Archives of Internal Medicine*, V. 15, pp. 444-450)
2. Weller, Carl V. Age Incidence in Sarcoma.
   (From *Archives of Internal Medicine*, V. 15, pp. 518-523)
3. Warthin, Aldred S. The Ideals and Functions of the International Association of Medical Museums.
   (From *The International Association of Medical Museums*, Bull. 5)
4. Warthin, Aldred S. On the Demonstration of Micro-Chemical Reactions in Museum Specimens.
   (From *The International Association of Medical Museums*, Bull. 5)
5. Weller, Carl V. The Use of Large Sections Mounted as Lantern Slides, as an Aid in Museum Teaching.
   (From *The International Association of Medical Museums*, Bull. 5)
6. Weller, Carl V. Cardiac Anomalies. Two Rare Cardiac Malformations.
   (From *The International Association of Medical Museums*, Bull., 5)
7. Weller, Carl V. The Blastophthoric Effect of Chronic Lead Poisoning: Breeding Experiments. Preliminary Report.
   (From the *Proceedings of the Society for Exper. Biology and Medicine*, V. 12, pp. 157-158)
8. Weller, Carl V. The Age-Relationship Between Types of Malignant Diseases.
   (From *The Journal of the Mich. State Med. Soc.*, V. 14, pp. 524-526)
9. Weller, Carl V. The Blastophthoric Effect of Chronic Lead Poisoning.
   (From *The Journal of Medical Research*, V. 33, pp. 271-293)
10. Weller, Carl V. Two Additional Cases of Miliary Tuberculosis of the Placenta with Clinically Latent Tuberculosis of the Mother.
    (From *Archives of Internal Medicine*, V. 17, pp. 509-515)
11. Warthin, Aldred S. and Wilson, Miss Unity F. The Coincidence of Latent Syphilis and Diabetes.
    (From *American Journal of the Medical Sciences*, V. 152, p. 157)

12. Warthin, Aldred S. Myxoma-Like Growths in the Heart, Due to Localizations of Spirochæta Pallida.
    (From *The Journal of Infectious Diseases*, V. 19, pp. 138-144)

13. Warthin, Aldred S. The Staining of Spirochæta Pallida in Tissues.
    (From *The International Association of Medical Museums*, Bull. 6)

14. Weller, Carl V. Some Substitutes for Glass for Covering Microscopical Sections. I. Gelatin. II. Pyralin.
    (From *The International Association of Medical Museums*, Bull. 6)

15. Warthin, Aldred S. Note on a Case of Complete Defect of Left Half of Diaphragm, Ectopia of Liver in Left Thoracic Cavity (Hernia Diaphragmatica Spuria) with Pressure Atrophy of Left Lung.
    (From *The International Association of Medical Museums*, Bull. 6)

16. Weller, Carl V. Coarctation of the Aorta with Patent Ductus Arteriosus.
    (From *The International Association of Medical Museums*, Bull. 6)

17. Weller, Carl V. Complete Uncorrected Transportation of Great Vessels without Defect in the Ventricular Septum.
    (From *The International Association of Medical Museums*, Bull. 6)

18. Dieterle, Robert R. Tubercle Bacilli in the Heart Clots in Acute Miliary Tuberculosis Complicating Chronic Lymphatic-Myelogenous Leukemia.
    (From *The Journal of Infectious Diseases*, V. 19, pp. 263-266)

19. Wilson, Unity Fletcher. Bacillemia in Tuberculosis as Shown by the Examination of Postmortem Clots from the Heart.
    (From *The Journal of Infectious Diseases*, V. 19, pp. 260-262)

20. Baker, Robert H., A.B. Cylindroma of the Tongue. With a Report of Two Cases.
    (From *Surgery, Gynecology and Obstetrics*, Sept. 1916, pp. 356-360)

21. Warthin, Aldred S. The Persistence of Active Lesions and Spirochætes in the Tissues of Cases of Clinically Inactive or "Cured" Syphilis.
    (From *American Journal of Medical Sciences*, V. 152, pp. 508-522)

The Occurrence of Malignant Neoplasms in the Young

AS SHOWN BY AN ANALYSIS OF 2,000 CASES OF MALIGNANT NEOPLASMS EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN

ALDRED SCOTT WARTHIN, M.D
ANN ARBOR, MICH.

Reprinted from the Archives of Internal Medicine
March, 1915, Vol. xv, pp. 444-450

CHICAGO
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
1915

THE OCCURRENCE OF MALIGNANT NEOPLASMS IN THE YOUNG

AS SHOWN BY AN ANALYSIS OF 2,000 CASES OF MALIGNANT NEOPLASMS EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN *

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

The present study is based on an analysis of 2,000 cases of malignant neoplasm contained in a total of 3,600 cases of neoplasm examined microscopically in the Pathological Laboratory of the University of Michigan during the years 1895-1913. This material is the same as that used in the two papers by Dr. Weller and myself[1] in THE ARCHIVES OF INTERNAL MEDICINE in 1913. As stated there, the material studied is a homogeneous one, derived almost entirely from the state of Michigan, and representing the average population of the state. Further, the material has been utilized not only for the purposes of practical diagnosis, but also in the teaching of pathologic histology, so that the percentage of error in diagnosis can be safely regarded as reduced to a minimum. This point is of especial importance, since the majority of statements concerning the occurrence of malignant neoplasm in the young are to be found in writings of the Virchow period when no exact differentiation of carcinoma and sarcoma was made, and when malignant teratoid tumors were classed as sarcoma or carcinoma or chondroma, etc., as the case might be, according to the preponderance of one or the other of the elements making up the growth. Doubt is, therefore, justly thrown on many of the diagnoses in the reported cases of congenital and early-life tumors. As Williams has mentioned, this is particularly true of the tumors described as "epitheliomata."

The age-period of 1 to 30 years has been chosen, as covering the entire period of development. It is of the greatest importance as far as the broad general neoplasm problem is concerned to establish the relations existing, if any, between the origin of neoplasms and the

---

* Read before the Association of American Pathologists and Bacteriologists, Washington, D. C., 1913.

* From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.

[1] Weller, C. V.: Age Incidence in Carcinoma, THE ARCHIVES INT. MED., 1913, xii, 539. Warthin, A. S.: Heredity with Reference to Carcinoma, etc., ibid., p. 546.

periods of bodily growth. The statement is frequently met in the literature that the development of malignant neoplasms is especially related to the climacterics. It is essential to know if such a relationship exists in the case of the lesser climacterics as well as of the grand. In the consideration of the occurrence of neoplasms in the young the first three decenniums should be taken as covering the periods of dentition, puberty, youth and early sexual maturity, if this question is to be settled. This has not yet been done. The greater number of the reports of malignant neoplasm has been concerned almost wholly with the question of *earliness*. Numerous cases of congenital and early-life neoplasms are recorded in the transactions of pathologic societies with reference to this one point; but little analysis has been made of collected cases from the more important point of view.

Of the 2,000 cases of malignant neoplasms studied, 195, or 9.75 per cent., occurred in the age-period 1 to 30 years. Of these 108 cases, or 55.4 per cent., were in males, and 87, or 44.6 per cent., in females (Table 1). The forms of neoplasms and their distribution through the thirty years is as follows:

AGE INCIDENCE

First Year

Rhabdomyosarcoma of kidney.
Round-cell sarcoma of orbit.
Lymphosarcoma of intestines.
Adenosarcoma of kidney, congenital.
Malignant teratoma of testis.
Angiosarcoma of eye.
Myxosarcoma of femur.
Congenital fibrosarcoma of neck.
Round-cell sarcoma of eye.
Spindle-cell sarcoma of jaw.
Adenorhabdomyosarcoma of kidney.

Second Year

Lymphosarcomatosis.
Angiosarcoma of eye.

Third Year

Small spindle-cell sarcoma of radius.
Rhabdomyosarcoma of kidney.
Spindle-cell fibrosarcoma of neck.
Lymphosarcoma of orbit.

Fourth Year

Lymphosarcoma.
Myxosarcoma of bladder.
Squamous-celled carcinoma of ear.
Rhabdomyosarcoma of testis.
Small round-cell sarcoma of eye.

Fifth Year

No cases.

Sixth Year

Lymphosarcomatosis.
Round-cell sarcoma of femur.

Seventh Year

Osteochondrosarcoma of femur.

Eighth Year

Spindle-cell sarcoma of orbit.
Large round-cell sarcoma of tibia.

Ninth Year

Large round-cell sarcoma of leg.
Fibrosarcoma of nose.

Tenth Year

Osteosarcoma of foot.
Spindle-cell sarcoma of eyelid.
Round-cell sarcoma of tibia.
Small round-cell sarcoma of orbit.

Eleventh Year

Squamous-celled carcinoma of leg.
Sarcoma of eye.
Lymphosarcoma of intestine.

Twelfth Year

No cases.

Thirteenth Year

No cases.

Fourteenth Year

Spindle-cell sarcoma of ulna.
Squamous-cell carcinoma of mouth.
Carcinoma of stomach.
Osteosarcoma of pelvis.
Adenocarcinoma of umbilicus (congenital).
Basal-celled carcinoma of eye.

AGE INCIDENCE—(CONTINUED)

FIFTEENTH YEAR

Adenocarcinoma of ovary.
Endothelioma of orbit.

SIXTEENTH YEAR

Osteochondrosarcoma of femur.
Alveolar sarcoma of tibia.
Large round-cell sarcoma of uterus.
Medullary carcinoma of ovary.
Large spindle-cell sarcoma of clavicle.
Osteosarcoma of tibia.
Osteochondroma of scapula.
Round-cell sarcoma of femur.

SEVENTEENTH YEAR

Spindle-cell sarcoma of tibia.
Sarcoma of parotid region.
Osteosarcoma of femur.

EIGHTEENTH YEAR

Basal-cell carcinoma of eye.
Malignant teratoma of ovary.
Osteosarcoma of humerus.
Colloid carcinoma of colon.
Round-cell sarcoma of skin of thigh.

NINETEENTH YEAR

Malignant teratoma of ovary.
Small round-cell sarcoma of orbit.
Alveolar round-cell sarcoma of ribs.
Large spindle-cell sarcoma of brain.
Spindle-cell sarcoma of bladder.
Metastatic carcinoma in cervical lymph-nodes.
Squamous-celled carcinoma of cheek.
Melanotic sarcoma of skin.

TWENTIETH YEAR

Colloid carcinoma of intestine.
Spindle-cell sarcoma of parotid.
Malignant syncytioma of uterus.
Malignant teratoma of testis.
Scirrhous carcinoma of stomach.
Fibrosarcoma of jaw.
Small spindle-cell sarcoma of jaw.
Spindle-cell sarcoma of face.
Fibrosarcoma of popliteal space.

TWENTY-FIRST YEAR

Squamous-celled carcinoma of cervix.
Myosarcoma of femur.
Basal-celled carcinoma of conjunctiva.
Lymphosarcomatosis.
Giant-cell sarcoma of ulna.

TWENTY-SECOND YEAR

Squamous-celled carcinoma of skin of abdomen.
Osteosarcoma of pubis.
Giant-cell sarcoma of jaw.
Lymphosarcomatosis.
Squamous-celled carcinoma of eye.
Small round-cell sarcoma of fibula.

TWENTY-THIRD YEAR

Squamous-cell carcinoma of skin.
Carcinoma of breast.
Lymphosarcomatosis .
Basal-cell carcinoma of eye.
Colloid carcinoma of cecum.

TWENTY-FOURTH YEAR

Adenocarcinoma of cecum.
Adenocarcinoma of breast.
Adenocarcinoma of ovary.
Osteochondrosarcoma of pelvis.
Alveolar round-cell sarcoma of neck.
Malignant teratoma of testis.
Fibrosarcoma of nose.
Malignant teratoma of testis.

TWENTY-FIFTH YEAR

Squamous-cell carcinoma of chin.
Medullary carcinoma of breast.
Malignant teratoma of testis.
Osteosarcoma of femur.
Lupus-carcinoma of face.
Lupus-carcinoma of cheek.
Melanotic sarcoma of skin.
Giant-cell sarcoma of jaw.
Myosarcoma of uterus.
Malignant teratoma of testis.

TWENTY-SIXTH YEAR

Sarcoma of skin.
Basal-cell carcinoma of lip.
Round-cell alveolar sarcoma of humerus.
Squamous-celled carcinoma of cervix.
Spindle-cell fibrosarcoma of jaw.
Fibrosarcoma of breast.

TWENTY-SEVENTH YEAR

Adenocarcinoma of uterus.
Carcinoma of antrum.
Spindle-cell sarcoma of breast.
Lymphosarcomatosis.
Medullary squamous celled carcinoma of cervix.
Squamous-celled carcinoma of lip.
Adenocarcinoma of uterus.
Squamous-celled carcinoma of hand.
Malignant teratoma of testis.
Adenocarcinoma of thyroid.
Squamous-celled carcinoma of cervix.

TWENTY-EIGHTH YEAR

Malignant teratoma of testis.
Cystocarcinoma of ovary.
Carcinoma of breast.
Squamous-called carcinoma of lip.
Rodent ulcer of eye.
Scirrhous carcinoma of pylorus.
Malignant teratoma of testis.
Medullary round-cell sarcoma of popliteal space.
Sarcoma of ovary.

Twenty-Eighth Year—(*Continued*)

Endothelioma of neck.
Malignant teratoma of testis.
Squamous-celled carcinoma of mouth.
Cystadenocarcinoma of breast.
Squamous-celled carcinoma of lip.

Twenty-Ninth Year

Spindle-cell sarcoma of femur.
Carcinoma of parotid.
Cystocarcinoma of ovary.
Endothelioma of orbit.
Squamous-celled carcinoma of penis.
Adenocarcinoma of tube.
Rodent ulcer of inner canthus.
Endothelioma of mouth.
Squamous-celled carcinoma of cervix.
Adenocarcinoma of rectum.
Squamous-celled carcinoma of cervix.
Basal-celled carcinoma of lip.
Medullary carcinoma of breast.
Basal-called carcinoma of nose.
Squamous-celled carcinoma of lip.

Thirtieth Year

Spindle-cell sarcoma of ovary.
Melanotic sarcoma of skin.
Spindle-cell sarcoma of heel.
Medullary carcinoma of cervix.
Endothelioma of chin.
Squamous-cell carcinoma of cervix.
Myosarcoma of cervix.
Lymphosarcoma.
Cystocarcinoma of ovary.
Myosarcoma of uterus.
Squamous-cell carcinoma of penis.
Medullary carcinoma of breast.
Carcinoma of breast.
Medullary carcinoma of cervix.
Medullary carcinoma of breast.
Lymphosarcomatosis.
Squamous-celled carcinoma of cervix.
Medullary carcinoma of cervix.
Adenocarcinoma of rectum.
Adenosarcoma of cervix, congenital.
Malignant syncytioma of uterus.
Lymphosarcomatosis.
Squamous-celled carcinoma of cervix.
Medullary carcinoma of breast.
Scirrhous carcinoma of breast.
Squamous-celled carcinoma of lip.
Cylindroma of parotid.
Squamous-celled carcinoma of leg.
Squamous-celled carcinoma of lip.
Myosarcoma of uterus.

The types of neoplasms were divided as follows: carcinoma 77, or 39.5 per cent.; sarcoma 92, or 47.3 per cent.; malignant teratoma 19, or 9.7 per cent.; malignant syncytioma 2, or 1 per cent.; endothelioma 5, or 2.5 per cent. If the malignant syncytioma and the malignant teratoma be added to the carcinoma, as all of the latter showed atypical epithelial proliferations, even in many cases to the extent of producing epithelial metastases of the nature of carcinoma, and as malignant syncytioma is epithelial in origin, it will be seen that the types of malignant neoplasms in this series are nearly evenly divided between connective-tissue and epithelial growths (Table 1).

TABLE 1.—Malignant Neoplasms, 2,000 Cases, in the Age Period 1-30 Years, 195 Cases, or 9.75 Per Cent.

	Cases	Per Cent.
Males	108	55.4
Females	87	44.6
Carcinoma	77	39.5
Sarcoma	92	47.3
Malignant Teratoma	19	9.7
Malignant Syncytioma	2	1.0
Endothelioma	5	2.5

Of the carcinomas the distribution as to locality was as follows: antrum 1, breast 12, eye and conjunctiva 7, small intestine 1, colon 1, cecum 2, rectum 2, lip 9, lymph-nodes 1, mouth 2, ovary 6, parotid 1, penis 2, tube 1, hand 1, leg 2, ear 1, cheek 2, nose 2, chin 1, elbow 1, stomach 2, pylorus 1, umbilicus 1, cervix of uterus 12, endometrium 2, thyroid 1 (Table 2).

TABLE 2.—SITE OF CARCINOMA

Antrum	1	Skin, back of hand	1
Breast	12	Leg	2
Eye, conjunctiva	7	Ear	1
Intestine	1	Cheek	2
Colon	1	Nose	2
Cecum	2	Chin	1
Rectum	2	Elbow	1
Lip	9	Stomach	2
Lymph-Nodes, metastatic	1	Pylorus	1
Mouth	2	Umbilicus	1
Ovary	6	Uterus, cervix	12
Parotid	1	Endometrium	2
Penis	2	Thyroid	1
Tube	1		

The distribution of the sarcomas with respect to site was: bladder 2, jaw 7, femur 10, tibia 6, fibula 1, heel 1, foot 1, pelvis 3, humerus 2, ulna 2, radius 1, rib 1, scapula 1, clavicle 1, brain 1, breast 2, eye 5, eyelid 1, orbit 5, face 1, intestine 2, lymph-nodes 10, muscle of abdomen 2, neck 4, nose 2, ovary 2, parotid 3, popliteal space 2, skin 5, body of uterus 4, cervix 2 (Table 3).

TABLE 3.—SITE OF SARCOMA

Bladder	2	Breast	2
Bone and Periosteum—		Eye	5
Jaw	7	Eyelid	1
Femur	10	Orbit	5
Tibia	6	Face	1
Fibula	1	Intestine	2
Heel	1	Lymph-nodes	10
Foot	1	Muscle, abdominal	2
Pelvis	3	Neck	4
Humerus	2	Nose	2
Ulna	2	Ovary	2
Radius	1	Parotid	3
Rib	1	Popliteal space	2
Scapula	1	Skin	5
Clavicle	1	Uterus	4
Brain	1	Cervix	2

The distribution of the malignant teratomas was: cervix of uterus 1, kidney 4, ovary 2, testis 12. The endotheliomas were distributed as follows: chin 1, orbit 2, mouth 1, neck 1 (Table 4).

TABLE 4

SITE OF MALIGNANT TERATOMA		SITE OF ENDOTHELIOMA	
Cervix uteri	1	Chin	1
Kidney	4	Orbit	2
Ovary	2	Mouth	1
Testis	12	Neck	1

The chart shows graphically the age distribution. It will be seen by this that the curve is high during the first year, falls then to rise at puberty, after which there is a steady rise up to the limit of the period, age 30. The large number in the first year emphasizes the importance of the *congenital factor*, and this influence is felt in the case of the majority of the tumors found up to the period of sexual ripeness, even when no actual evidences of a teratoid nature could be demonstrated in the tumor. Sarcoma predominates in the period of infancy and childhood; but the *parallel increase of both sarcoma and carcinoma with age is noteworthy and in contradiction to the usual belief that sarcoma is essentially a disease of childhood.* The cases of malignant teratoma fall in the periods of early childhood and developing sexual life. Particularly is this the case with the malignant teratomas of testis and ovary, the majority of these cases developing after puberty and in the early period of sexual maturity. No especial relationship to the period of dentition is shown. We had no cases in the fifth year, and none in the twelfth and thirteenth years. The number of cases in the years 6 to 11 is too small to show any conclusion. The main facts shown by the chart are the relatively high number of congenital tumors, the gradual increase in incidence of tumors from the age of adolescence into mature life, the relation of malignant teratomas to puberty and the parallel incidence of carcinoma and sarcoma.

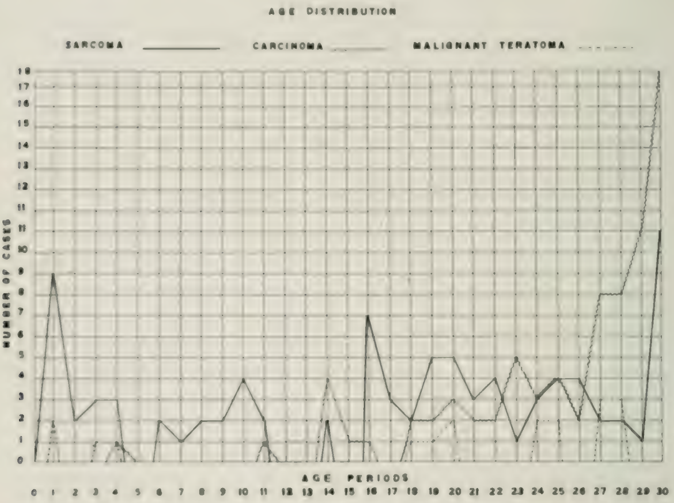

Chart showing age distribution of sarcoma, carcinoma and malignant teratoma.

---

2. Williams: The Natural History of Cancer, 1908.

The best analysis of congenital and early-life neoplasms is that by Williams.[2] The analysis of our 195 cases of malignant neoplasms of this period differs in a number of ways from his. His analysis is based on Duzan's analysis of 182 malignant tumors of early infancy, Picot's analysis of 424 cases, his own of 56 consecutive cases, Poinsot's 25 cases of bone sarcoma in infancy, Gross' study of sarcoma of the long bones (51 cases) and 41 cases tabulated by Butlin and Colby. Williams points out the relative frequency of retinal glioma and renal tumors as congenital. No retinal glioma occurs in my series, and only four cases of congenital neoplasm of the kidney. Likewise the tendency to sarcoma observed by him on the part of the scapula is not shown in our series, only one case being included.

Williams concludes that prenatal life, infancy and childhood are wholly exempt from malignant epithelial tumors. He rejects many of the reported cases as untrustworthy. He gives the earliest age at which carcinoma has been positively demonstrated as 11 years (columnar-celled cancer of rectum). He himself saw a case of rodent ulcer at 14 years. He asserts that under the age of puberty cancer is practically unknown. In our list we find an undoubted and typical squamous-celled horny cancer of the lobe of the ear at 4 years (no evidence of teratoid origin could be found) ; at 11 years a typical horny squamous-celled carcinoma of the skin of the leg; in the fourteenth year an adenocarcinoma of the umbilicus (teratoid in origin), a typical squamous-celled carcinoma of the mouth, a basal-celled carcinoma of the eye and an adenocarcinoma of the stomach. Our list then gives undoubted examples of earlier carcinoma than those recorded by Williams. He also reports the earliest examples of cancer of the breast as occurring at 20.5 and 21 years. Our list gives two operated on in the twenty-third year, the tumors having begun to develop before the twentieth year.

My conclusions in the main agree with those of Williams. Malignant tumors are relatively rare before puberty, but there is a steady ascending line of occurrence from childhood onward to middle life, *both sarcoma and carcinoma showing a parallelism of occurrence.* This fact is also strikingly brought out in the study of sarcoma by Dr. Weller. Our cases in a large measure also support Williams' view of the *congenital or teratoid origin of malignant neoplasms in infancy and early life.*

The tendency to malignant tumors is relatively slight before sexual maturity is reached, increases during the period of sexual maturity, up to the age-period of 58 to 62. With the decline of the organism the tendency to malignant neoplasm decreases.

AGE INCIDENCE IN SARCOMA

CARL VERNON WELLER, M.D.
ANN ARBOR, MICH.

Reprinted from the Archives of Internal Medicine
April, 1915, Vol. xv, pp. 518-523

CHICAGO
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
1915

AGE INCIDENCE IN SARCOMA *

CARL VERNON WELLER, M.D.
ANN ARBOR, MICH.

In a previous statistical study[1] it was shown that the incidence of carcinoma is greatest at the age period 58 to 62, and that there is a definite decrease in carcinoma incidence after this period. In the present report it is proposed to treat by a similar method a large group of sarcoma ages obtained from the same source, hoping in this way to contribute to the knowledge of the biologic relationship between the two types of malignant disease.

In the past it has been the custom of both pathologists and surgeons to find in age incidence one of the chief points of difference between carcinomas and sarcomas. The usual statement of text-books has been that carcinoma is a disease of the old and sarcoma of the young. Da Costa[2] says that sarcomas may arise at any period from birth to extreme senility, but that they are commonest during youth and early middle age. On the other hand, Williams several years ago,[3] and again more recently,[4] has declared that this differentiation between carcinoma and sarcoma cannot be made. His conclusions are quoted in full:

> The sarcomata may arise at any period of life; a certain number of cases are congenital; more are met with in early infancy, especially during the first five years, than at any other period prior to the twentieth year; after which sarcomata increase in frequency until middle life, becoming rarer again in old age.
>
> It will be gathered from what I have stated that there are close analogies between the two diseases — sarcoma and carcinoma — such differences as are noticeable being due to diversity of origin and its consequences, rather than to any essential difference in the nature of the morbid process.

Williams found that he could derive the same conclusion either from the onset ages as taken from hospital records or from mortality returns.

As will be seen, our analysis of 265 consecutive cases of sarcoma bears out these conclusions in practically every particular. The method which has been used is the same as that employed in the preparation of the previous report[1] on age incidence in carcinoma. Therefore, it

---

* From the Department of Pathology, University of Michigan.

[1] Weller: Age Incidence in Carcinoma, THE ARCHIVES INT. MED., Chicago, 1913, xii, 539-545.

[2] DaCosta: Modern Surgery, 1910, p. 365.

[3] Williams: Twentieth Century Practice of Medicine, 1898, xvii, 487.

[4] Williams: The Natural History of Cancer, 1908, p. 323.

will not be necessary to repeat it in detail here. The material from which these figures were derived consists of the consecutive cases of sarcoma of known age diagnosed in the pathological laboratory of the University of Michigan between the years 1895 and 1913. The advantages which this material possesses over either cancer censuses or mortality returns may again be briefly outlined. These data are derived

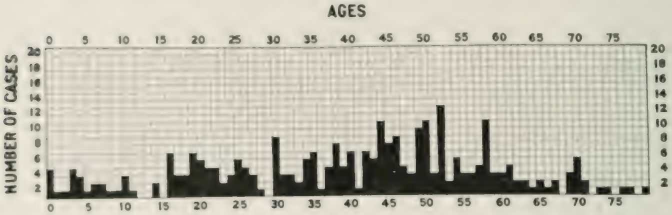

Chart 1.—Age distribution of sarcoma.

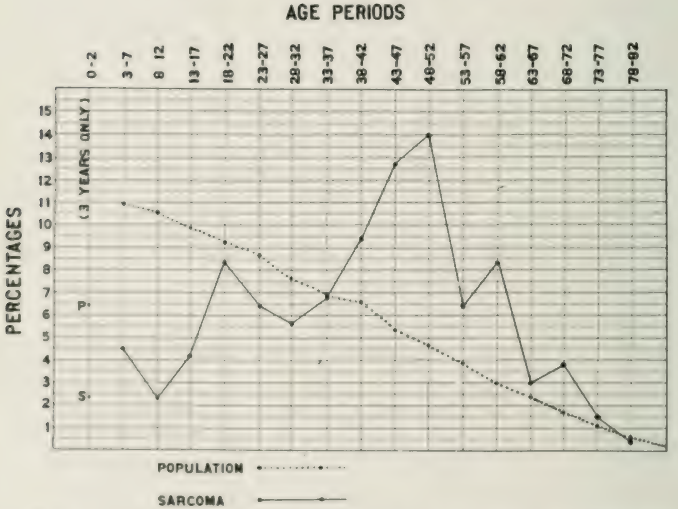

Chart 2.—Percentage of sarcoma cases for each age period contrasted with the percentage of total population living at each age period.

from a representative fraction of the population of Michigan and the neighboring states; the ages are given at an earlier stage of the disease than is possible in either of the other types of statistics; and each case has had complete microscopical verification. The figures for the age distribution of the total population are taken from the United States

Census Report[5] for 1900. Since less than 10 per cent. of these cases of sarcoma came from without the state of Michigan, it has been possible to use the age distribution of the population of Michigan alone without introducing any appreciable error.

The yearly distribution of the ages of the total 265 cases of sarcoma is shown by Chart 1. As was the case with a similar chart showing carcinoma ages, the years which are multiples of five, and also, in a lesser degree, the even years, are favored by patients in giving their ages. For instance, there are ten cases at age 50 and twelve at age 52, while only three patients gave 51 as their age and only two are found at 53. This error of approximate answers has been overcome almost entirely in all subsequent charts by the simple device of grouping all figures in age periods of five years each with the multiple of five as the middle year in each group. From Chart 1 it should be noted that the number of cases of sarcoma is comparatively small until age 16 is reached, and that the greatest number of cases in any one year falls at age 52.

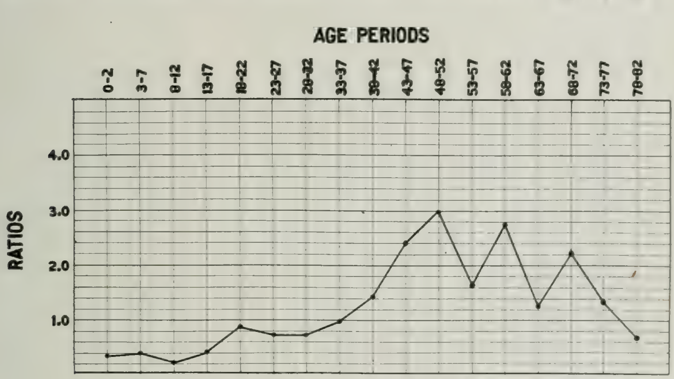

Chart 3.—Corrected curve of age incidence of sarcoma obtained by plotting a series of ratios between the percentages used in Chart 2.

In Chart 2 the percentage of the total number of sarcoma cases for each age period is graphically contrasted with the percentage of the total population which is living at each age period. The sarcoma curve lies below the population curve until age 35 is reached. It then remains above the population curve until extreme old age is reached, at which period the proportion of the population found to be living and the number of sarcoma cases alike become too small to permit of drawing trustworthy conclusions. Stated in another way, these curves indicate that up to age 35 the incidence of sarcoma is less than it would be were sarcoma uniformly distributed throughout the entire population; that at age 35, the point of crossing of the two curves, the incidence of sarcoma is the same as it would be were sarcoma uniformly distributed throughout the total population, and that after age 35 sarcoma is much more prevalent than a uniform distribution would lead one to expect. Now the curve of *carcinoma* percentages was found to cross the curve of population percentages at age 37, and thus there is found to be an almost exact coincidence of the points of crossing in the two types of malignant disease. This close analogy in respect to age distribution will be more completely demonstrated in another chart.

---

[5] Report, Twelfth Census, U. S., 1900, ii, Part 2, p. 52.

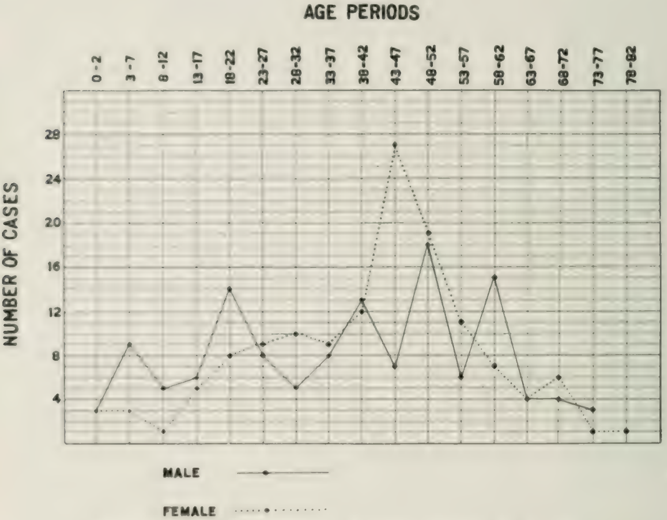

Chart 4.—Age distribution of sarcoma divided as to sex.

In Chart 3 the data embodied in Chart 2 are handled in a somewhat different way. The sarcoma curve of Chart 2 does not in itself give a true curve of age incidence for sarcoma, because of the decreasing population in each successive age period. In Chart 3 a corrected curve of age incidence is obtained by plotting a series of ratios between the percentages used in Chart 2. For instance, the

$$\text{Ratio for age period N} = \frac{\text{percentage of sarcoma for age period N}}{\text{percentage of population for age period N}}$$

From the true curve thus obtained it appears that the incidence of sarcoma is relatively low until the period of puberty is reached. At that time there is a moderate increase, and this higher level is maintained until age 30. There is then a rapid rise until age period 48 to 52 is reached, at which point is found the maximum incidence of the disease. After this period the ratios again decrease until they become less than one in extreme old age. The fluctuations of this portion of the curve are due in part to the marked degree in which patients favored the multiples of ten in giving their ages, and in part to the smaller number of cases to be found at each age period, since with figures for the number of cases and for the population both relatively very small, slight variations cause correspondingly greater fluctuations in the curve.

If sarcoma were uniformly distributed in respect to age incidence, the ratio for each age period would be unity. This chart (No. 3) shows that the actual incidence is below this level throughout the first half of life and above unity throughout the second half of life. It is, therefore, impossible to speak of sarcoma as a disease of the young. It is frequent in the young, but most common in late middle life.

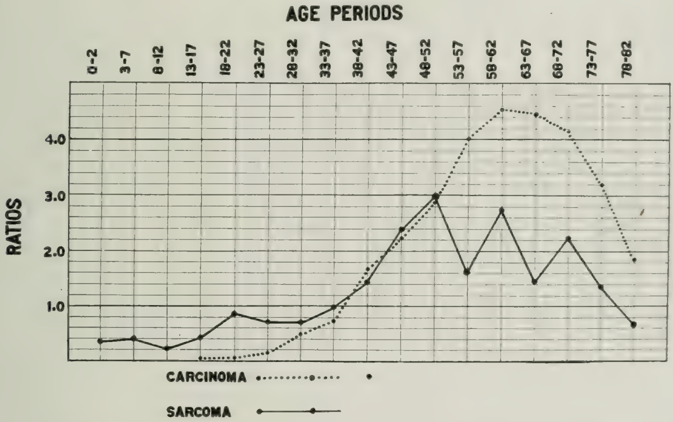

Chart 5.—Corrected curves of age incidence of carcinoma and sarcoma.

In Chart 4 the age distribution of our sarcoma cases, divided as to sex, is shown. Of the total 265 cases, 129 occurred in males and 136 in females. When these are arranged according to age periods, there is a rough parallelism between the two curves. This would doubtless be more perfect if a larger number of cases were under consideration. The apex of the curve of cases in females is at age period 43 to 47. This is of interest for the apex of the curve of female carcinoma cases also occurred at this age period. Unlike carcinoma, however, these curves do not definitely indicate any earlier incidence of sarcoma in females than in males. This was to have been expected, for in the previous report it was shown that the earlier cycle of carcinoma incidence in females is largely determined by the carcinomas of the breast and uterus, organs which early undergo involution changes. These two sources provided more than two-thirds of all our cases of carcinoma in women. In the anatomical distribution of sarcoma no such powerful factors are introduced.

On Chart 5 are plotted the fully corrected curves of age incidence of carcinoma and of sarcoma. The carcinoma curve is reproduced from the report to which reference has previously been made. The great similarity of the two curves is evident, but the most striking feature is the almost perfect coincidence of the two curves from age period 28 to 32 up through age period 48 to 52. Although the sarcoma incidence in the young is higher than the carcinoma incidence, it still remains less than unity, and so age incidence, instead of affording a means of contrast or differentiation, serves but to emphasize the biologic similarity between the two great types of malignancy.

In conclusion, the analysis here given indicates that:

1. The incidence of sarcoma is greatest at the age period 48 to 52. Therefore, sarcoma can no longer be considered a disease of the young.

2. After this period the sarcoma incidence gradually decreases.

3. There is no marked difference in the age distribution of sarcoma in males and in females.

4. Although in youth sarcoma incidence is somewhat higher than carcinoma incidence, there is throughout life a marked parallelism between the age incidence curves for the two types of malignancy, and for more than twenty years there is a practical coincidence, thus strongly suggesting that the causal or predisposing agencies in the two cases must either be identical or, at least, have much in common.

The Ideals and Functions of the International Association of Medical Museums

PRESIDENT'S ADDRESS
XVII International Congress of Medicine
London, August, 1913

ALDRED SCOTT WARTHIN, PH.D., M.D.
Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan.

REPRINTED FROM THE INTERNATIONAL ASSOCIATION
OF MEDICAL MUSEUMS, BULLETIN NO. V
JUNE 1, 1915

THE IDEALS AND FUNCTIONS OF THE INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUMS

PRESIDENT'S ADDRESS

XVII International Congress of Medicine
London, August, 1913.

Aldred Scott Warthin, Ph.D., M.D.,
University of Michigan, Ann Arbor.

With this meeting in London, held in conjunction with the XVIIth International Congress of Medicine, the International Association of Medical Museums enters upon the seventh year of its existence, and achieves its second international triennial meeting. From its small beginnings as a little group of pathologists and anatomists especially interested in demonstrative and objective teaching, the society has grown into a membership of over two hundred, and contains on its rolls the names of the majority of the world's leading workers in pathology and anatomy. It has initiated and conducted a number of successful and highly interesting meetings, all of these, up to the present time, having been held in the United States under the auspices of the American branch. Today's meeting is the first one to be distinctly international in character, and through it it is hoped that the Association may complete its international organization, and enter upon that broader field of work and influence we believe to be peculiarly its own.

It is fitting at this time to bring up for discussion the ideals and functions of this society and to determine its especial right to existence. The unceasing multiplication of new associations may well make us hesitate before launching another venture. It has become an all-too-common thing for any small body of individuals having a certain community of thought and interests to become convinced of its own especial need for a separate and close organization. Undoubtedly the lines demarcating many of these organizations are a little too finely drawn and without thorough justification. The demands made upon any medical worker, even moderately successful in his line, for membership fees and dues, contributions to programs, expenses of attending meetings, subscriptions to journals and bulletins have become undoubtedly burdensome; and the expressed wish is often heard that the number of societies be diminished rather than increased. With this point of view I am wholly in sympathy; but I believe that the Association of Medical Museums does meet a need that no other existing organization attempts to fill, and that this need is not the narrow one of a small and limited body of specialists of the medical museum alone, but that of *the whole broad field of objective and demonstrative teaching*. This to my mind constitutes the peculiar function of this society, and its ideals should be the thorough working of this field. In achieving this its endeavors should be carried along the five following lines: 1, The Medical Museum; 2, The Research Museum; 3, The Public Museum; 4, Methods of Technique; 5, Methods of Demonstrative Teaching. These will be discussed in order.

1. The Medical Museum.—The original plan of the founders of this association contemplated, perhaps, no greater field of activity than that of the museum of the medical school, a collection of typical and rare pathological and anatomical specimens and preparations to be utilized in the didactic activities of the school. All that pertained to the preservation and mounting of such specimens in the best and most illustrative manner, methods of preserving color, injection, the manner and arranging of exhibits, types of museum cases, labelling, cataloguing, etc., were considered to lie within its especial province, and papers and demonstrations of this kind formed the subject matter of the presentations and exhibits made at the earlier meetings of the association. The society was also to serve as a medium of exchange of specimens between different museums.

The importance of the *medical museum* in the teaching of medicine cannot be over-estimated, but such museums have been sadly neglected by the present generation of medical teachers in the United States at least. Not one of the better-class medical schools has any museum worthy of it. The valuable collections of our predecessors, while consisting largely of anatomical preparations, bones, monsters and other spectacular specimens, have been allowed to disappear as the result of neglect and indifference, and nothing better has taken their place. The anatomical collections are usually much better than the pathologic, but no one of our schools has a medical museum comparable to that of McGill, and few of them attempt any museum demonstrative teaching.

That our medical teaching loses in effectiveness because of the lack of proper museums and museum teaching we must admit. It may be explained by the over-accentuation of research and investigation, and the demands made upon medical teachers in this direction at the expense of thorough medical teaching. But the fact that this association had its birth in the United States and has steadily grown there may be taken as proof of an increasing interest in the development of the medical museum. To McGill University directly we are indebted for the inspiration that led to its foundation. This society should serve then as advisor and guide in developing and stimulating such museums; it should act as a clearing house for the exchange of experiences in matters of museum technique and museum teaching, and as a medium of exchange between museums.

II. The Research Museum.—There should be developed also museums or collections of the material used in research by workers of a given country or from the whole world. Original or duplicate preparations, slides, records, photographs, drawings, etc., should be collected at central or easily accessible bureaus where other workers can study them or compare them. Useless duplication of work would thus be avoided, and a better control of results obtained. From the historical side such research collections would also be of great value. Rare specimens can be seen and studied, comparisons made, and differences in interpretation checked by means of such collections. The value to both general and special students of such research exhibits as the embryological series accessible in the collections of Minot, Mall, and Huber of Ann Arbor cannot be over-estimated. Records of the development and evolution of ideas in any branch of medicine, as in the case of new surgical instruments or new operative procedures, new diagnostic methods, new appliances, etc., would form suitable material for such research museums.

III. The Public Medical Museum.—The efforts of this association cannot stop with the teaching and research museums of the medical schools. Today another and as important a field lies before us inviting our coöperation and earnest endeavors:—the field of public instruction through museums and exhibits illustrating all of those facts concerning health and disease that should be the intellectual possession of every human being, if disease is to be finally conquered and driven from the earth. During the last decade there has advanced with gigantic strides, almost magically, the conception of the prevention of disease, a philosophy and a truth appealing to the human mind as no other idea has ever done. The public health campaigns instituted by those who have been the first to realize the meaning of *preventive medicine* have from the very first used as their chief educational means the illustrative and demonstrative teaching methods of the museum. The anti-tuberculosis campaign throughout the entire world has carried on its most effective educational work through the tuberculosis exhibits. Following the International Congress on Tuberculosis held in 1908, a tremendous impetus was given to such popular museum teaching throughout the United States. Not only has tuberculosis in all of its aspects been presented thus objectively and demonstratively to the layman's mind, but likewise the propaganda against malaria, typhoid fever, infant mortality, milk infections, infant blindness, occupational diseases, venereal diseases, and all the other preventable diseases have been effectively presented through the medium of public exhibits and museums.

Such popular teaching museums have been instituted by physicians who have seen the truth and have had the vision; they have been developed by various associations and societies started by the enthusiasm of such medical men. Today the local and State Boards of Health have taken up such educational work and are carrying it on in a most effective manner. In a number of the central states the travelling exhibit has been developed as a part of the educational work of such boards. Cars or even entire trains forming museums representing the most important facts of personal and public hygiene and preventive medicine are regularly sent on tours along the railroad lines traversing the state, stops being made at every village, town and city on the line. The success of these travelling exhibits has been wonderful, and the response from the public proves beyond any doubt the legitimacy of such educational museums and the appreciation of such exhibits.

I believe that in America, at least, there is a tremendous future for the Public Medical Museum. The ignorance of the average layman about his own body is almost pathetic, and accounts for the strong hold upon the lower classes exercised by the so-called anatomical museum of the quack-doctor. How much better it would be for humanity if every large city possessed a scientific municipal museum with one section—a chief one— devoted to an explanation and exposition of the human body, as well as of the facts relating to the prevention of diseases! Few things at the Hygienic Congress in Dresden attracted so much favorable mention from medical visitors or gave so much impressive teaching to laymen as the building devoted to the human body, which contained exhibits explaining in detail the gross and microscopic structure of the human organism, its physiologic functions, the processes of reproduction and development, etc., all shown in the clearest and most objective manner. No wonder that crowds constantly awaited their turn to see this wonderful exhibit. I believe that few things would do more for the good of the race than such an exhibit placed in every large city.

In the initiation of such popular museum teaching and in the preparation of such exhibits this association has the most vital interest and should take an active part. Such museums must have the most careful planning, they must possess the most accurate scientific data, and they must have the constant supervision of men of scientific medicine. They cannot be left to the layman alone, or even to the man who has had only a public health education. Everything that concerns objective and demonstrative medical teaching and museum technique must be applied to these popular medical museums; and this association has a duty in respect to the development and management of such museums that it cannot afford to neglect, if it reaches its fullest measure of usefulness. I believe that in America the State Universities should take first place in the development of such educational museums, and the trend in this direction is already shown by the active participation of University Extension departments in the public health propaganda.

IV. Microscopic Technique.—Closely associated with museum technique and with the technical methods employed in museum teaching is the whole field of microscopic technique. Surely research in this direction is as important as in other lines of so-called pure research. It will be impossible for the latter to advance without the constant invention and discovery of new technical methods. There should be some especial recognition of this fact and some especial association is needed to stimulate investigation in this direction. I do not know of any other society today in which methods of microscopical technique are given a prominent place in programs and in discussions. It is also difficult to find a suitable place for the publication of purely technical articles; and in the usual pathological association or medical society papers dealing exclusively with technical matters are not encouraged.

I believe that this association should enter this field and combine the discussion of microscopic technical methods with those of museum technique. So closely do the two touch each other that there is no logical separation, and the need for a clearing house of microscopic methods is as great as that for museum methods. That this is true is shown by the program presented at this meeting and by the great demand for a symposium on microscopic technique similar to the one conducted a year ago in our Bulletin on museum technique. The numerous questions relating to microscopic technique that have been sent in with reference to individual experience along certain lines show that there are many workers who would be glad to establish a common interest in technical matters and who would be glad of the aid given them by an association that would encourage the free discussion and publication of methods of microscopical technique. In America at least there is a definite need for the help which this association can give in this direction through its bulletin.

V. *Methods of Medical Teaching.* As the final field suitable to the activities of this association, I would suggest that of medical pedagogy. Surely the teaching of medicine and its improvement and evolution are as important as the development of any branch of medical science. There exists today no society in which the science and art of medical teaching are taken up and discussed. Very few articles upon medical teaching appear in the medical journals. There is no branch of teaching about which so little is written and said as there is about medical teaching. That there exists a definite need for some vehicle through which medical pedagogy can obtain recognition I myself do not doubt. Whenever a group of medical teachers get together informally, discussion as to teaching methods inevitably arises, and the vague and unsatisfactory way in which such discussions are carried on shows clearly the need for some more general clarifying medium. At the meeting in Chicago a year ago the general trend of the meeting was accidentally turned along lines of medical education, and the energetic and forceful way in which the discussion of teaching principles and methods was taken up and the general satisfaction resulting from the opportunity of such free discussion showed clearly this need. I think therefore we may with profit extend the scope of this organization so that it may include not only the methods of objective and demonstrative teaching associated with the museum but also all of the problems associated with medical teaching.

These, in brief, form my conception of what the ideals and functions of the International Association of Medical Museums should be. I believe that there is a special need for such an association, that in entering this field it will not in any way be as a trespasser upon preserves already occupied, but as a pioneer in fulfilling what has never before been attempted, not only in methods and matters purely related to the medical museum but along wider sociologic lines, as well as medical ones at the present unsatisfactorily developed. We need everywhere larger and better museums, both medical and public. The public medical museum is bound to come; it is now even arising, but it must be controlled and developed by medical men rather than by laymen, and medical men must have the proper knowledge and experience for the satisfactory development of such museums. In such work this association can offer the greatest possible aid and can be of the greatest possible value.

We have met today with another object in view, the completion of our international organization. It seems particularly fitting that this association, dealing as it does with such general questions as medical education and objective teaching, should be placed upon an international basis. Particularly is this necessary if we enter the broader sociologic field of public health museums. Such matters concern the whole world. The sanitary housekeeping of any one nation concerns the sanitary housekeeping of the whole world, and the questions of public health and the education of laymen to an intelligent comprehension of such constitute an international problem. Experience of workers from the entire world must be collected and correlated. And it is along such lines that the international function of this association should be developed.

THE ANN ARBOR PRESS

On the Demonstration of Micro-Chemical Reactions in Museum Specimens

Aldred Scott Warthin, Ph.D., M.D.,
Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan.

Reprinted from The International Association
of Medical Museums, Bulletin No. V
June 1, 1915

ON THE DEMONSTRATION OF MICRO-CHEMICAL REACTIONS IN MUSEUM SPECIMENS.*

A. S. WARTHIN.

Pathological Laboratory, University of Michigan.

Great aid may be given to the teacher in general pathology and particularly to museum demonstration through gross preparations showing various micro-chemical reactions. It is possible with some care and ingenuity to make preparations that will show to the naked eye the more important micro-chemical reactions such as amyloid, calcification, fatty infiltration, fatty degeneration, mucin, connective tissue hyalin, fibrosis, and the various pigmentations. Among the most striking of all are the beautiful preparations that can be secured with the aid of the newer fat dyes, Sudan III, Scharlach R., etc. The number of recent papers concerning the demonstration of fatty changes in gross preparations by means of these dyes shows the coincidence of discovery in widely scattered laboratories of the value of such preparations. My first preparations with the fat dyes were made as early as 1903 with aortas stained with Sudan III and Scharlach R. to show the fatty changes in the intima. Before that time, however, I had made beautiful preparations showing the Berlin blue reaction in organs in a state of haemosiderosis. The beauty and the permanency of these preparations led me from time to time to attempt other demonstrations of specimens showing various micro-chemical reactions. Many of these have been failures, while others have aided greatly in the efficiency of teaching work. My best results, however, have been obtained in the demonstration of iron pigment and in the use of the various fat dyes. I give here a very brief survey of the possibilities in this line, a field as yet but slightly worked.

1. *Haemosiderosis.*—Beautiful preparations of pernicious anaemia liver, spleen, lymph nodes and bone marrow, malarial liver and spleen, all the organs from cases of general haemochromatosis, organs from cases of acute haemolytic poisoning such as

---

*Read at the meeting of the American Section of the International Association of Medical Museums, St. Louis, 1915.

potassium chlorate, infections with bacillus pyocyaneus and haemolytic streptococci, organizing haematomata, old extravasations, organizing thrombi, etc., may be made by fixing the tissues first in alcohol or formol, then treating not too thick slices for some hours in a saturated solution of potassium ferro-cyanide, then for several hours in a 1% solution of hydrochloric acid until the blue is well developed, thorough washing in water, and preservation in 4% formol. Any teacher having access to a large autopsy material can ultimately acquire a beautiful series of cases illustrating all the varieties and phases of iron pigmentation.

Ammonium sulphide and hydrogen sulphide preparations can also be made, but the black color is not as striking to the eye in gross preparations and is not permanent. I have several Berlin blue preparations over ten years old and as bright as when they were first made. Haemosiderosis of the haemolymph nodes in Banti's disease and in pernicious anaemia can be well shown by this method. Many of these preparations of lymph nodes I have converted into gelatin preparations; but the blue color shows somewhat better in the wet specimens.

2. Preparations of organs and tissues containing fat stained with Sudan III or Scharlach R. may be produced as most striking aids in teaching. Among the many preparations possible are aortas showing atheroma and fatty degeneration, fatty degeneration and fatty infiltration of the heart, liver, and kidneys, lipomatosis of the pancreas, kidney, parotid, sub-maxillary gland and striped muscles, elephantiasis lipomatosa, sections of breast tumors and cysts, sections of small lipomata, etc. Material should be fixed first in formol; formol washed out after a few days; put into alcohol for a few hours or shorter time, especially if small; then stained in bulk in alcoholic or acetone solutions of Sudan III or Scharlach R. for one to several days; then wash thoroughly in water, differentiate in alcohol, and preserve in 4% formol. Fatty degeneration and infiltrations can be beautifully differentiated in this way, also the types of fat. Cholesterol esters, and other lipoids give a different color, more brown, than that obtained with the glycerin esters. The studies of the changes in the blood vessels obtained by these preparations are also most striking and instructive.

Very good osmic acid preparations can also be produced, particularly of the fatty infiltrations.

3. Von Kossa's method can be applied to the gross demonstration of lime salts.

4. Weak solutions of acid fuchsin can be used to demonstrate connective tissue hyalin and fibrosis. Counter-staining with haematoxylin may be used to bring out the contrast. The most beautiful results, however, are obtained by applying the Van Gieson method to tissues showing connective tissue hyalin, such as the ovary, hyaline myofibromata, cylindromata, laparotomy scars, contracted kidney, healed tubercles, hyaline goitres, etc. The material should first be stained in bulk in Weigert's iron haematoxylin, then in the Van Gieson mixture of concentrated water solution of picric acid and acid fuchsin until the rose-red color of the hyalin stands out sharply. Very instructive pictures can be made of sections of the entire ovary, the stain bringing out most beautifully the corpora fibrosa and corpora lutea. The picric acid, however, is lost in fluid permanent preparations, but is preserved for a longer time in jelly. Beautiful preparations of colloid and hyaline goitres may be made by this same method. It is better, however, to preserve these in balsam.

5. My experience with amyloid has not been very successful, none of my preparations lasting more than two years when exposed under ordinary conditions to the light. My best results were obtained with the Birch-Hirschfeld method, using a 20% gentian violet solution and contrasting with Bismarck brown. Slabs of amyloid liver, spleen and kidney preserved in syrup will make good preparations for two years. Other metachromatic reactions and the iodine reaction last but a very short time. In the case of the iodine reaction the mahogany brown color may be preserved longer by keeping the material in iodine vapor.

These are but hints and suggestions of the possibilities of this hitherto unworked field in the teaching of pathology and museum demonstration. It is one of the side paths that may be taken up by the progressive teacher in his effort to drive home lasting impressions of important pathological conditions.

THE ANN ARBOR PRESS

The Use of Large Sections Mounted as Lantern Slides, as an Aid in Museum Teaching

By Carl Vernon Weller, A.B., M.D.
Instructor in Pathology, University of Michigan

Reprinted from The International Association
of Medical Museums, Bulletin No. V
June 1, 1915

THE USE OF LARGE SECTIONS MOUNTED AS LANTERN SLIDES, AS AN AID IN MUSEUM TEACHING.*

By Carl Vernon Weller, A.B., M.D.,
Instructor in Pathology, University of Michigan.

The gap between the microscopical slide and the gross specimen is one which the average medical student has much difficulty in bridging. This difficulty is largely due to two factors: the small size of the microscopic field and the difference in the types of illumination in the two cases.

Even with the lower powers of magnification than those ordinarily used, the microscopic field still remains so small that the student has great difficulty in recognizing the grosser relationships. In fact, the entire section cut from such blocks as are found to be of convenient size for routine diagnostic and teaching work oftentimes provides too small an area to assist greatly in interpreting the gross specimen in terms of the microscopical picture. The difficulty is increased by the fact that the impressions produced by transmitted and by reflected light are often not easily reconciled.

In the case of pathologic lesions which possess moderately gross structural characteristics, we have found that these difficulties may be in some degree overcome by the use of stained sections:—

1. Large enough to preserve the structural relationships which it is desired to emphasize, and
2. Thin enough to be viewed by the naked eye as semi-transparencies or to be identified with the lower powers of the microscope.

We have found it desirable to mount these large sections in such a manner that they may be projected directly as lantern slides. In this form they may also be conveniently passed from hand to hand, or may be displayed in the museum, either as opaque or as semi-transparent object, in connection with the gross specimen from which they are derived.

---

* Read at the meeting of the American Section of the International Association of Medical Museums, St. Louis, Mo., April 1st, 1915.

Concerning the technical methods employed very little need be said, for the cutting and staining of sections, such as we are doing, in itself offers nothing new or unusual. All of our sections have been cut from paraffin infiltrated tissues with a range of thickness of from ten to forty microns. If the preparations are intended chiefly for museum display it is better not to cut sections thinner than twenty or twenty-five microns. Either direct fixation upon the slide with egg albumin, or molasses fixation with transfer to a celloidin sheet, may be used with equal success. If many sections are to be prepared at one time, molasses or dextrin fixation is much to be preferred.

The staining may be of whatever nature the specimen demands. We have used haemalum and eosin routinely In the interest of economy, we have mounted our sections upon old lantern slides from which the emulsion has been removed by boiling. The xylol used in the final cleaning is carefully blotted away and clear balsam, rendered more fluid by warming, is applied. The cover glasses are those everywhere used for covering lantern slides. These are warmed before applying and the excess balsam is then carefully pressed out. This may be done easily in a turntable clamp such as is used in taping lantern slides. Before putting on the binding strips it is well to let the preparation harden for several days. The advantage in this is that it makes it possible to correct any retraction of the balsam from the edges of the glass plates. With a hard balsam, however, very little difficulty will be found with the formation of air spaces through retraction of the balsam. This difficulty means that too thin a balsam is being used.

This method is especially useful when the pathologic lesions have rather gross relationships. It accordingly finds ready application in demonstrating the extent and character of the extensions of malignant processes, large tuberculous foci, gummata, cystic change, large areas of infarction, haemorrhage, hypoplasia, and hyperplasia of organs, and many other gross lesions.

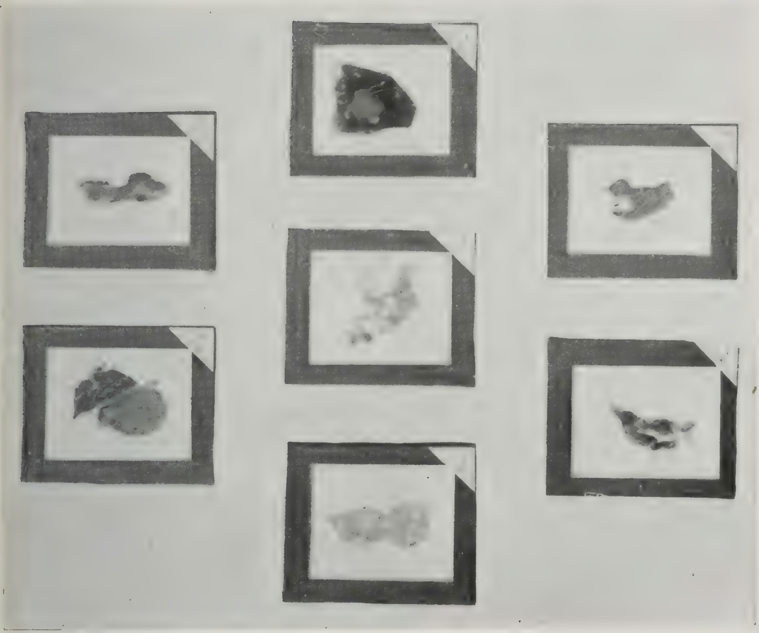

Fig. 1.—Large Tissue Sections Mounted as Lantern Slides

THE ANN ARBOR PRESS

CARDIAC ANOMALIES

TWO RARE CARDIAC MALFORMATIONS

By Carl Vernon Weller, A.B., M.D.
Instructor in Pathology, University of Michigan

Reprinted from The International Association
of Medical Museums, Bulletin No. V
June 1, 1915

Cardiac Anomalies

TWO RARE CARDIAC MALFORMATIONS:

(1) *Congenital Aneurismal Dilatation of the Ductus Arteriosus;*
(2) *True Partial Transposition of the Great Vessels with Both Aorta and Pulmonary Artery Arising from the Right Ventricle.*

By Carl Vernon Weller, A.B., M.D.,
Instructor in Pathology, University of Michigan.

1. *Congenital Aneurismal Dilatation of the Ductus Arteriosus.*

In Dr. Abbott's[1] analysis of 631 cases of congenital cardiac disease there occurs a small group of thirteen cases in which the ductus arteriosus was found to be dilated to such a degree that the condition was described as an aneurism or an aneurismal dilatation. The present case falls into this group but differs from most of the others in that there was no evidence of thrombosis of the dilated ductus.

The patient, a male infant 5 days old, was born in the Maternity Ward of the University Hospital, (service of Dr. Peterson). The delivery was normal and the baby appeared to be in excellent condition, crying spontaneously. There was no cyanosis worthy of note. On the third day the child has a temperature of 102° and on the fourth day there was blood in stools and vomitus and hemorrhages from mouth and navel. These were repeated on the fifth day, on which the infant died. The Wasserman was negative on both mother and child and no history of haemophilia could be obtained, but the mother had only one living male relative.

Aside from the condition of the heart the autopsy findings were quite negative except for multiple sub-serous hemorrhages and a marked passive congestion.

The heart itself measured 4.5 by 3.5 by 2.8 cm. Both ventricles were firmly contracted. The wall of the left ventricle averaged 5 mm. in thickness; the right, 7 mm. The inter-ventricular septum was complete and there were no anomalies of the valve cusps. The foramen ovale was patent to but the normal degree for the age of the subject, admitting a 3 mm. probe. The aorta measured 5 mm. in diameter 1 cm. above the valve, while the diffusely dilated pulmonary artery measured 12 mm. in diameter at the same level.

---

[1] Abbott. Osler-McCrae, Modern Medicine, Vol. iv, p. 341.

Lying above the heart and bulging anteriorly between the aorta and the pulmonary artery there was found a rounded mass the size of a cherry. This proved to be the patent and greatly dilated ductus Botalli which retained its rounded contour somewhat in spite of the fact that it was practically empty. The total length of the ductus was about 3 cm. and it was thrown into a tortuous course best described as a reversed letter "S." The first portion of the curve, near the aorta and convex anteriorly and to the left, formed the bulging tumor first noted. Here the lumen of the empty ductus was 1 cm. in diameter. The second portion of the ductus, concave anteriorly and near its junction with the pulmonary artery, was much more narrow and had a lumen 6 mm. in diameter.

No other anomalies were found either in the viscera or elsewhere in the body.

The specimen may be classified as one of aneurismal dilatation of the ductus arteriosus, unassociated with other anomalies except a diffuse dilatation of the pulmonary artery.

2. *True Partial Transposition of the Great Vessels with Both Aorta and Pulmonary Artery Arising from the Right Ventricle.*

The second heart is that of a male infant, four weeks old, who was a patient in the Department of Paediatrics of the University Hospital (service of Dr. Cowie). The child had not been cyanotic but a diagnosis of congenital cardiac disease had been made, based upon auscultatory findings.

Death followed operation for cleft palate and at autopsy in addition to the various anomalies present there was found to be an acute purulent meningitis, an acute purulent pyelitis and metastatic abscesses in lung and kidney. Body length was 45 cm., weight, 2120 gms.

A striking feature of the case was the number and variety of malformations and defects present. There was a complete double cheilopalatoschisis, and a sacro-coccygeal dimple, well-marked, with a hairy border. There was cryptorchismus and the penis was diminutive in size. The pinnae of both ears were unusually wide. The fore-fingers of each hand lacked the terminal phalanx and there was no nail formation upon these fingers. The nail of the great toe of the right foot was but rudimentary. Anomalies were found also in examining the viscera. The right lung was divided into but two lobes and there were two accessory spleens, while the heart presented the interesting condition which makes it the subject of this report.

The heart measures 3.5 by 3 by 2 cm. There is a single apex formed equally by both ventricles.

The left ventricular wall measures 3-5 mm, in thickness and this cavity communicates with the left auricle through an orifice which is guarded by a large anterior and a small posterior cusp. From this ventricle there is no exit by an arterial trunk but it communicates with the right ventricle through a defect in the inter-ventricular septum 5 mm. in diameter. This defect is situated in the base of the septum in such a position that it is partially covered by the large anterior cusp of the mitral valve. The left auricle receives the pulmonary veins.

The right ventricular wall measures 5-7 mm. in thickness. From this ventricle two arterial trunks are given off. The larger of these, which lies to the right, is the aorta. It gives off the great vessels from the arch in normal order. The opened aorta has a circumference of 21 mms. The aortic valve consists of two well-marked cusps and the larger of these shows an imperfect sub-division. Considered as three cusps the right anterior cusp is the non-coronary one.

Also from this ventricle and to the left and slightly posterior to the aortic valve a pulmonary artery is given off. This is much smaller than the aorta and measures 13 mm. in circumference. Although arising to the left of the aorta, the pulmonary artery passes spirally behind it so that the bifurcation of the pulmonary is almost directly behind the aorta. The pulmonary valve is bicuspid.

The ductus Botalli is patent, admitting a 2 mm. probe. The foramen ovale is also quite widely open, measuring 7 mm. across.

The right auricle receives the venae cavae. It is guarded by a bicuspid valve, the cusps of which are irregular in size. The right auricular appendage is given off to the right of the auricle.

Because of the multiple anomalies, the classification of this heart is a matter of some difficulty. It shows a transposition of the great vessels amounting to somewhat less than a 180° rotation. This transposition is but imperfectly corrected by the interventricular septum so that both arterial trunks are given off from the right ventricle. This anomalous arrangement of the great vessels is associated with a defect in the inter-ventricular septum, with an open foramen ovale and with a patent ductus arteriosus.

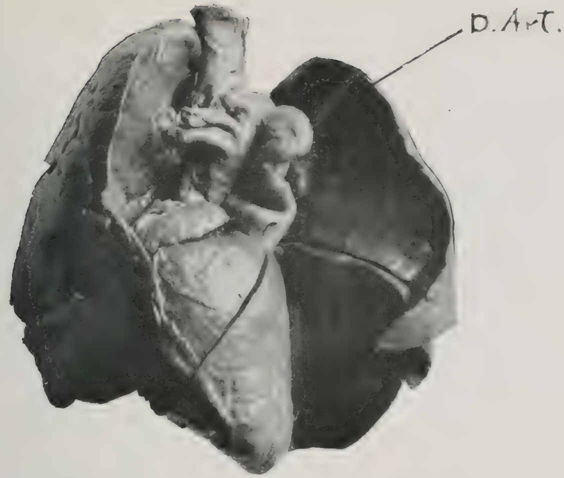

Fig. 1.—Congenital Aneurismal Dilation of the Ductus Arteriosus, *D. Art.*—the Ductus Arteriosus Bulging Anteriorly and to the Left of the Arch of the Aorta.

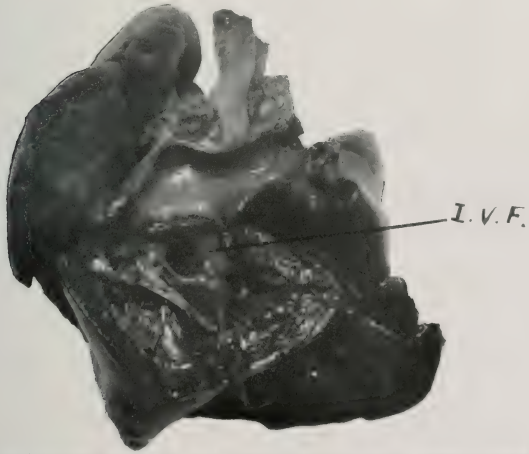

Fig. 2.—Transposition of the Great Vessels with Both Aorta and Pulmonary Artery Arising from the Right Ventricle. *I. V. F.*—the Foramen in the Interventricular Septum.

THE ANN ARBOR PRES

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,
1915, xii, pp. 157–158.

93 (1025)

The blastophthoric effect of chronic lead poisoning: Breeding experiments. Preliminary report.

By **Carl Vernon Weller, A.B., M.D.** (*by invitation.*)

[*From the Department of Pathology, University of Michigan.*]

There have been frequent clinical observations of the apparent deleterious effect upon the germ plasm exerted by chronic lead poisoning. A majority of these cases have been found in female lead workers and in these it might be supposed that abortions, stillbirths and early deaths of infants were due as much to the toxic effect of lead during intra-uterine development as to an actual injury to the germ plasm. In the smaller number of instances in which the male parent alone was poisoned, the resulting sterility without impotency, the stillbirths and the early deaths of offspring are difficult to explain unless they are due to blastophthoria. The work of Stockard and of Cole and Davis has shown that alcohol has a similar effect. In a recent report which appeared as the present series of experiments was being concluded Cole and Bachhuber have demonstrated that the offspring of male rabbits poisoned by lead as well as of male fowls similarly poisoned are of distinctly lower vitality than the offspring of normal males.

In attempting to determine experimentally whether blastophthoria occurs in chronic lead poisoning, guinea pigs were given repeated weighed doses of commercial white lead in capsules by mouth. These guinea-pigs were mated, lead females with normal males and lead males with normal females. In order to check the results as efficiently as possible control matings were made of normal males with normal females under the same feeding and housing conditions as the lead poisoned pigs, and for the same reason the normal females were bred alternately to lead males and to normal males. The dosage of lead was controlled by frequent weighings in order that the general nutrition should not be seriously impaired.

A total of 93 matings yielded 170 offspring. Of these, 32 matings of normal male with normal female produced 58 offspring with an average birthweight of 81.5 gms. From 34 matings of lead male with normal female 65 young were produced with an average birthweight of but 66.3 gm. From 27 matings of normal male and lead female, 47 young were produced with an average birthweight of 69.3 gm. Nine offspring of lead males died in the first week against two offspring of normal males dying in that time. Eight young of lead females were stillborn against three stillborn from normal females bred to normal males.

From the entire series of matings the following conclusions seem to be justified:

1. In chronic lead poisoning in guinea pigs there is a definite blastophthoric effect which can best be demonstrated upon the male germ plasm. This effect manifests itself in some instances by sterility without loss of sexual activity, by a reduction of 20 per cent. in the average birthweight, by an increased number of deaths in the first week of life and by a retardation in development such that these pigs remain permanently underweight.

2. From the apparent recovery of the germ plasm some time after stopping the administration of lead it seems that the deleterious effect must be suffered especially by that portion of the germ plasm which is undergoing maturation and not by that which is stored in the primary germinal epithelium. However, final judgment upon this point must be withheld.

Reprinted from
The Journal of the Michigan State Medical Society
October, 1915
F. C. Warnshuis, Editor, Grand Rapids

The Age-Relationship Between Types of Malignant Diseases

CARL VERNON WELLER, A.B., M.D.
Instructor in Pathology, University of Michigan.
(From the Pathological Laboratory of the University of Michigan, Ann Arbor, Michigan.)

Now that the theory of a definite family tendency toward malignant disease has received both clinical and experimental verification to a surprising degree, the attack upon the cancer problem has been directed more than ever before along purely biologic lines. The recognition of the fact that some purely intrinsic factor is concerned, to an extent as yet unmeasured, in the origin of malignant disease has given to the study of the natural history of the neoplastic cell a new and well merited interest. This report deals with one phase of that subject, the relationship between the ages at which the two great types of malignant disease, carcinoma and sarcoma, make their appearance.

On purely *a priori* grounds one would be led to expect that the age distribution of carcinoma and of sarcoma would be found to be much the same, for the two conditions are essentially similar. Each is characterized by the power of unlimited and uncontrolled cell multiplication, while the greatest apparent difference between them depends merely upon definition of terms in that carcinomas are derived from epithelial structures and sarcomas from the supporting tissues of the body.

Nothwithstanding the apparent analogy between the two types, the belief has been rather widely held that in respect to age distribution there is a marked difference between carcinoma and sarcoma. Carcinoma has long been considered a disease of late middle life and senility and sarcoma a condition affecting particularly the young but occurring to some extent at any age. This view has found expression in textbooks and throughout medical literature. For instance, De Costa (1) says that sarcomas may arise at any period from birth to extreme senility, but that they are commonest during youth and early middle age. On the other hand, Williams, several years ago (2), and again more recently (3), has emphasized the fact that sarcoma does not widely differ from carcinoma in its age distribution and that the two types of malignancy exhibit close biologic analogies. His conclusions are so nearly substantiated by the work which I shall present that they are here quoted in full:

"The sarcomata may arise at any period of life; a certain number of cases are congenital; more are met with in early infancy, especially during the first five years, than at any other period prior to the twentieth year; after which sarcomata increase in frequency until middle life, becoming rarer again in old age.

"It will be gathered from what I have stated that there are close analogies between the two diseases—sarcoma and carcinoma—such differences as are noticeable being due to diversity of origin and its consequences, rather than to any essential difference in the nature of the morbid process."

Upon the material which was received at the Pathological Laboratory of the University of Michigan during the years 1895 to 1913 a diagnosis of carcinoma was made in 1106 cases of known age. As a basis for a statistical study this material possesses certain advantages over either mortality returns or the results of a cancer census in that every case has received microscopic verification and that the age of the patient is obtained at a much earlier stage of the disease than in mortality records. Thus the true age incidence is more accurately represented. In a previous paper, (4) the age data from these 1106 cases have been graphically analyzed and compared with the age distribution of the total population of Michigan. After proper correction for the variations in the total population for different age periods the true curve of carcinoma incidence was determined. It was found that up to age 37, the incidence of carcinoma increases gradually until, at that age, it reaches the point at which the incidence is the same as it would be were carcinoma uniformly distributed throughout the entire population. From this point the rise is rapid until the apex of the curve is reached at age period 58 to 62. The incidence of the disease is then 4.5 times as great as it would be were carcinoma uniformly distributed at all ages, but from this point on the curve falls very definitely, indicating an actual reduction in carcinoma incidence in the later years of life.

Similarly, there were diagnosed in the Pathological Laboratory of the University of Michigan, between the years 1895 and 1913, 265 cases of sarcoma of known age. These have been graphically analyzed by the same method as that used in studying the age data of the carcinoma series (5). The fully corrected curve of sarcoma incidence shows a relatively low level until the period of puberty is reached. At this time there is a rather sharp increase, but the ratio of percentage of sarcoma to percentage of population does not become unity until age 35. That is to say, previous to age 35 the incidence of sarcoma is less than it would be were sarcoma uniformly distributed throughout the entire population. Conversely, after the age 35 there must be found an extensive period in which the incidence of the disease is considerably above the mean. Such is the case, for the ratios of sarcoma incidence remain above unity until the eighth decade and are at their highest level in age period 48 to 52 at which point sarcoma is three times as prevalent in our series as it would be were the disease met with equal frequency at all ages.

Sarcoma cannot, therefore, be considered a disease of the young. While it may, and does, occur at all ages, sarcoma, like carcinoma, has its greatest incidence in middle life. This parallelism is shown to a remarkable degree when the corrected curves of carcinoma and sarcoma incidence are superimposed and compared period by period. It is then found that the two curves not only have the same general contour throughout but, in fact, almost exactly coincide for a period of over twenty years, from age period 28 to 32 to age period 48 to 52. The points upon the two curves corresponding to a ratio equal to unity (the points at which the incidence of the two types is the same as it would be were they each equally prevalent at all ages) are but two years apart. Remarkable as this parallelism is, there is reason to believe that it would have been even more complete had the age data in regard to sarcoma been derived from a larger group of cases.

In conclusion, analysis of the age distribution of this relatively large series of microscopically verified carcinomas and sarcomas shows a marked analogy between the two types of malignancy. As judged from this aspect, it appears that the malignant process must be essentially the same no matter in what type of tissue it may develop and that the causal or predisposing agencies in the two types of malignancy must either be the same or, at least, have much in common. Attention is called to the fact that malignant neoplasms of purely teratomatous origin, whether carcinomatous, sarcomatous, or mixed in cell type, will not conform in an equal degree to the rule of age incidence for malignancy as given above; for the usual measures of age become meaningless when applied to teratoid structures.

REFERENCES.

(1) De Costa: Modern Surgery, 1910, p. 365.

(2) Williams: Twentieth Century Practice of Medicine, 1898, XVII, p. 487.

(3) Williams: The Natural History of Cancer, 1908, p. 323.

(4) Weller: Age Incidence in Carcinoma. Archives of Inter. Med., XII, pp. 539-545.

(5) Weller: Age Incidence in Sarcoma. Archives of Inter. Med., XV, pp. 518-523.

THE BLASTOPHTHORIC EFFECT OF CHRONIC LEAD POISONING

CARL VERNON WELLER, A.B., M.D.
(From the Department of Pathology, University of Michigan, Ann Arbor, Michigan)

Reprinted from
The Journal of Medical Research, Volume XXXIII., No. 2
(New Series, Vol. XXVIII., No. 2), pp. 271-293, November, 1915

BOSTON
MASSACHUSETTS
U.S.A.

THE BLASTOPHTHORIC EFFECT OF CHRONIC LEAD POISONING.*

Carl Vernon Weller, A.B., M.D.

(*From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.*)

1. Introduction. Clinical and Experimental Observations from the Literature.

It is now well known that certain disease conditions deleteriously affect the germ plasm of both the male and the female of the human species. This blastophthoric effect, even though it may occur in some infectious diseases such as typhoid fever, is quite apart from the transference of the infecting agent to the germ cells. In fact, it has been convincingly demonstrated that toxic substances of non-infectious origin, notably alcohol, are equally capable of producing a blastophthoria of a marked degree.

Since this type of injury implies the possibility that purely external and extrinsic etiological factors may so work upon the germ plasm that the resulting changes are manifest as intrinsic disease, the recognition of the agents producing such changes becomes of the greatest importance from the standpoint of practical eugenics. Unless the injury to the germ plasm is of such a character that the perpetuation of the line is prevented or limited through its own feebleness, it is reasonable to expect that the intrinsic change wrought in the germ plasm may be shown by a departure from the normal through many generations. Such a blastophthoric effect has been attributed to chronic lead poisoning. In this case the problem assumes additional interest since it deals with one of the most common forms of occupational disease. If it can be shown that the clinical observations of lead blastophthoria are supported by experimental evidence an additional argument of unusual weight will be added to the

---

* Received for publication Aug. 12, 1915.

many excellent reasons already existing for considering this one of the most serious of the occupational diseases. The injurious effect of plumbism will then be measured as much by the deterioration of the family line as by the impairment of the health of the individual

In 1860 Constantin Paul[1] stated that lead poisoning of the mother, or even of the father, often results in the stillbirth of the fetus; and that the children of such parents, when born alive, usually die in the first three years of life and have but feeble resistance to disease. His attention was called to this disastrous effect upon the progeny of those suffering from chronic lead poisoning by the case of a woman who had been delivered of 3 living and healthy children previous to exposure to lead. Subsequently, she became pregnant 10 times and these 10 pregnancies were terminated by 8 abortions, 1 stillbirth, and 1 child which was born alive at term but died at the age of 5 months.

From this and many similar cases Paul accumulated extensive data in regard to the effect upon the offspring of lead intoxication of the mother. These figures have been frequently quoted in works upon Occupational Diseases, but are well worth repeating here. Of 141 pregnant women, working in lead, 82 aborted, 4 had premature births, 5 had stillborn infants and 50 brought living children to term. Of these 50, however, 35 died in the first two years of life, so that from 141 pregnancies but 15 children survived to the third year.

More important still as indicating a true lead blastophthoria are Paul's observations upon the progeny of fathers suffering from lead poisoning. He found that 32 pregnancies in 7 women whose husbands were lead workers and had shown signs of lead poisoning gave 11 abortions, 1 stillbirth, and 20 living children. Of the 20 living children, however, 8 died in the first year, 4 in the second year, 5 in the third year, and 1 after the third year. Thus but two individuals remained alive as the product of 32 pregnancies. As a result of these observations Paul concluded that the influence of lead as transmitted to the offspring from the father is just as real as when derived from the mother, but is perhaps a little less deleterious, the reason for this being that in the mother the intoxication produces its effect upon the organism not alone at the moment of conception, but also throughout the duration of pregnancy.

Sir Thomas Oliver[2] reports an epidemic of stillbirths in a Yorkshire town which called for an unofficial inquiry. The cause was found to be the contamination by lead of the drinking water supplied the town. With the removal of the cause, the effect ceased.

He also quotes Dr. George Reid's[3] statistics upon the relationship between lead poisoning and miscarriages, stillbirths, and early death of infants. These figures are as follows:

For 100 mothers, engaged in housework,	43.2	miscarriages and stillbirths.
For 100 mothers, engaged in millwork, not lead,	47.6	" " "
For 100 mothers, lead workers before marriage,	86.0	" " "
For 100 mothers, lead workers after marriage,	133.5	" " "
For 100 mothers, father a lead worker,	48.0	" " "

In regard to early death of infants:

Deaths under 1 year per 1,000 births:

Mothers engaged in housework,	150
Mothers, mill workers, not lead,	214
Fathers alone working in lead,	189
Mothers working in lead before marriage,	157
Mothers working in lead after marriage,	271

Oliver likewise verified the observations of Chyzzer[4] upon the conditions in the home potteries of Hungary. In some villages he found practically no children, while the inferior physical and mental development of the offspring of these pottery workers led him to conclude that infantilism, idiocy, and mental weakness were some of the effects of "inherited plumbism." Deaths from hydrocephalus, acute meningitis, and convulsions were frequently noted among these children.

Oliver found that of the children of paint grinders 40 per cent die of convulsions during the first year of life.

Thompson[5] has collected many of the important observations in regard to lead blastophthoria, including those of Paul and Oliver. He refers to the fact that lead has been found in the placenta and in the kidneys and liver of stillborn children of mothers who were lead workers. He quotes also from the French Department of Labor Report on Industrial Poisons, made by M. Tardieu in 1905, who found that of 1,000 pregnancies in lead workers 608 terminated in abortion; and also from P. Rudeaux,[6] who states that out of 442 pregnancies among the wives of 75 lead workers, there were 66 abortions and 241 miscarriages.

Goadby[7] concludes that there is little evidence for supposing that a male lead worker is less likely to beget children, or that his children are more likely to be unhealthy than those of men working in any other industrial process, provided that modern methods are employed to prevent absorption. "In the absence of any precautions whatever as to daily absorption of dangerous dust, the effect on the offspring, even in the case of male lead workers, may well be evident."

The experimental evidence of a blastophthoric effect in chronic lead poisoning has not been abundant. The results obtained by Oliver[2] working with fowls and rabbits have been much quoted.

"If fowl's eggs be incubated after painting the shell of some of them with a strong solution of lime and the shell of others with a solution of lead nitrate, I found that, while all those that had been painted with lime came to maturity, from not one of those painted with lead nitrate did there come forth a live chick. On opening the egg, the embryo was always found to have reached a fair stage of development. . . . Similarly in the case of pregnant rabbits, to whom lead was administered in food, miscarriage took place, and in the internal organs of the fetuses lead was found on chemical examination."

Thompson [6] quotes the work of Charron, who investigated the possibility of chronic lead poisoning from deep chrome yellow and bright red papers found to contain lead. Pregnant guinea-pigs, confined in cages lined with these papers, aborted and the fetuses contained traces of lead in their organs.

Legge and Goadby [7] state that all the pregnant animals to which they gave lead aborted, and that experimental results confirm the well-known abortifacient action of diachylon. They refer to similar results obtained with guinea-pigs by Glibert [8]

As the series of breeding experiments which forms the second part of this report was being concluded the work of Cole and Bachhuber [9] appeared, constituting the most important experimental contribution to the subject of lead blastophthoria up to that time. They administered lead acetate, mixed with sugar of milk and fed in gelatin capsules. Animals thus poisoned were bred by a system of double mating such that the offspring by means of color or other characteristics could be identified as derived from either a normal or a lead-poisoned male. Rabbits and fowls were used and in each case their results led to the conclusion that the offspring produced by males which had been poisoned by the ingestion of lead acetate into the alimentary tract were of a lower vitality and that in the case of the rabbits such offspring were distinctly smaller in average size than the normal offspring of unpoisoned males.

Much of the clinical and experimental evidence is suggestive rather than demonstrative of a lead blastophthoria. In many cases one cannot rule out the effect upon the embryo in utero of lead intoxication in the mother as an important factor apart from and in addition to the injury to the germ plasm of the parent. Likewise, acquired plumbism may explain some of the results seen in the children in the home potteries. But with due allowance for such cases the evidence seems highly in favor of a true lead blastophthoria. The observations of Paul and Rudeaux upon the offspring of lead-poisoned fathers and the experimental work in which lead was administered to the male animal are especially valuable as offering an apparently incontrovertible line of evidence.

2. Breeding Experiments.

In an attempt to prove or disprove the occurrence of a true blastophthoria in chronic lead poisoning, a series of breeding experiments extending over a period of eighteen months was undertaken. The changes in the male germ plasm in particular were investigated as being of the greater value in this connection, since, when the injury is directed toward the male element alone, the possibility of injury to the developing embryo through pre-natal poisoning or through impaired nutrition growing out of its implantation in the body of a diseased female does not exist. Accordingly, the general method of attacking the problem was to produce a condition of chronic lead poisoning in male animals, to breed these males to normal females and to compare the results of these matings with those of control animals under similar housing and feeding conditions. In addition, female animals were also poisoned with lead and bred to normal males in order to obtain data for comparison.

Administration of lead and determination of dosage. — In order to duplicate as nearly as possible the most common method of acquiring saturnism as an occupational disease, commercial white lead was chosen as the form to be administered. This was given to guinea-pigs by mouth in weighed doses in No. 5 gelatin capsules. Very little difficulty was met with from this method of administration and it seemed quite necessary to employ it in order to have a more definite dosage than is possible when the poison is mixed with food. The capsules, moistened with water, were placed in the animals' mouths by means of a small glass tube fitted with a glass rod plunger. Usually the capsules were masticated before swallowing and only occasionally were they rejected.

In preparation for filling the capsules, a known weight of commercial white lead was brought to a paste of proper consistency by mixing it with linseed oil and corn starch. The weight of this mixture was then obtained and the capsules were also weighed before and after being filled with it. From this data the average dose of commercial white lead was computed. For instance, in preparing a certain batch of capsules 27.25 grams of commercial white lead were mixed with enough linseed oil and starch to make a total weight of 65.45 grams. With this paste, two hundred and fifty No. 5 gelatin capsules were filled. These weighed 7.57 grams when empty and 34.50 grams when filled. The two hundred and fifty capsules therefore contained 26.93 grams of the lead paste which was $\frac{27.25}{65.45}$ commercial white lead. The average dose of commercial white lead for this batch of capsules was therefore $\frac{1}{250} \times \frac{27.25}{65.45} \times 26.93$ grams $= .045$ gram.

The variation in the body weight of the guinea-pigs was found to be the most satisfactory guide to the intensity with which the white lead was administered and the size and frequency of the dose were changed accordingly. Care was taken that there should be no marked loss of weight in the pigs under observation and any such drop in weight was taken to be the indication for reducing the size of dose, increasing the interval between doses or temporarily suspending the administration of lead. This precaution was taken to avoid the possibility that an apparent lead blastophthoria might in reality be due to the impaired nutrition and cachectic state of the pigs if the poison were pushed too severely. That this was not the case is shown by Figures 1 and 2, which give a graphic comparison of body weight and lead dosage for a period of about five months in two representative lead poisoned guinea-pigs. It will be seen that one, a young growing female, gained two hundred and fifty grams during that period and that the other, a mature male, weighed sixty grams more after five months than when the lead was first given. In some cases there were sudden reductions in weight such that no lead could be administered for several weeks. In a few others, epileptiform convulsions were induced even when there had been no loss of weight and following the convulsive attacks such pigs were so ill

LEAD FEMALE 3.

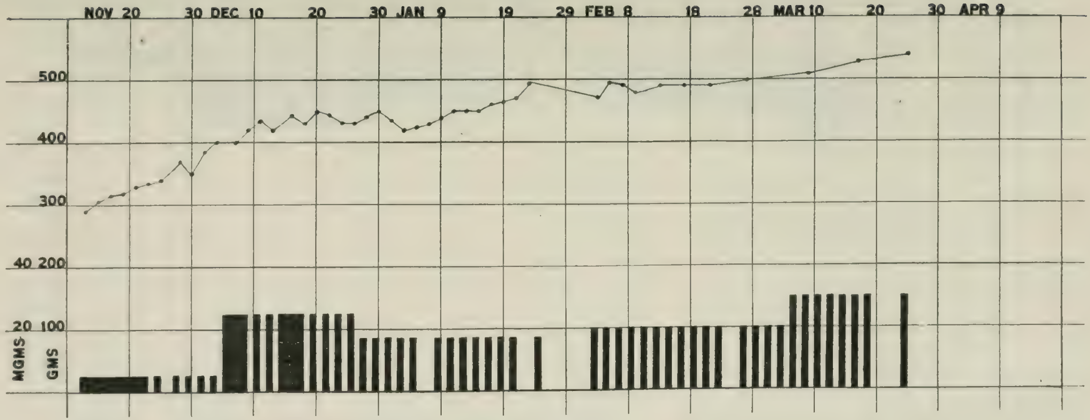

FIG. 1.

Graphic comparison between the weight curve and the dosage of white lead in a young growing female. A gain of 250 grams is shown in spite of the administration of 66 doses of white lead ranging from 5 to 30 milligrams each.

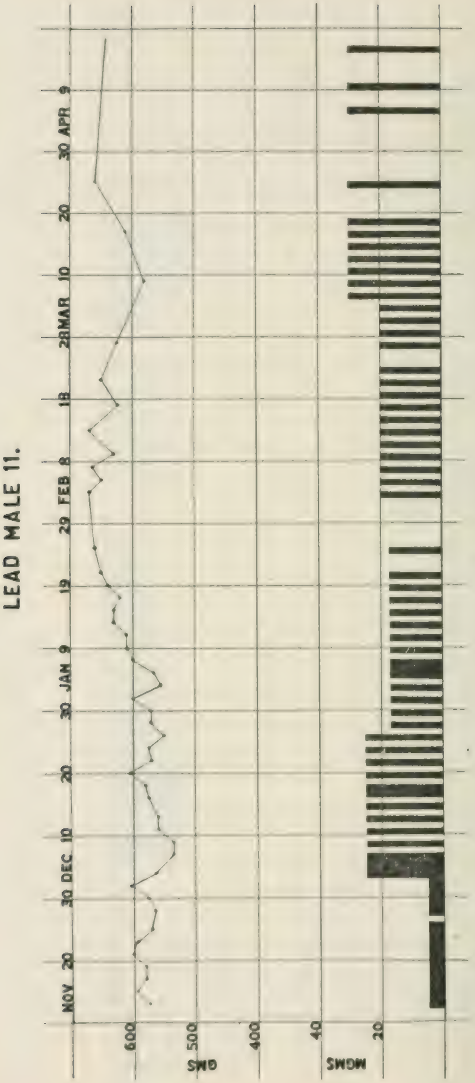

Fig. 2.

Graphic comparison between the body weight curve and lead dosage in an adult male guinea-pig. A gain of 60 grams is shown in spite of the administration of 75 doses of white lead ranging from 5 to 30 milligrams each.

that no lead was given for several days. With these exceptions lead was administered every other day throughout the greater part of the period covered by the experiment. Undoubtedly, had the lead been pushed more vigorously, the injury to the germ plasm would have been more severe and the results of breeding experiments more spectacular, but conclusions as to the blastophthoric effect of lead, per se, could then be drawn with much less certainty.

The amount of commercial white lead given at each administration was made to vary from six to eighty-two milligrams. The following table shows the number of doses, the period over which they were distributed and the total amount of commercial white lead received by a few pigs selected as representing the general character of this phase of the experiment.

TABLE I.

	Number of Doses Received.	Duration of Administration.	Total Amount of Commercial White Lead Received.
Female G.P. No. 3......	95	11 months.	2.310 grams.
" " " 12.......	106	11 "	2.479 "
Male " " 11.......	109	9½ "	2.660 "
" " " 17.......	52	3½ "	1.163 "
" " " 26.......	129	12 "	4.679 "
" " " 44.......	91	8½ "	3.992 "
" " " 50.......	95	8 "	4.016 "

Matings. — Guinea-pigs thus chronically poisoned with lead were mated, lead females with normal males and lead males with normal females. In addition, a series of matings of normal males with normal females was maintained at the same time and under the same housing and feeding conditions as for the lead-poisoned pigs. An additional check upon the results was obtained by subsequently breeding the normal females, which had given birth to offspring by lead-poisoned males, to normal males. Thus we were enabled to rule out the possibility that an apparent blastophthoric injury to the male parent was but an expression of an intrinsic fault in the germ plasm of the supposedly normal female. Some of our most interesting results were obtained by means of this method of breeding a female alternately to a lead-poisoned and to a normal male.

Summary of results of breeding experiments. — A total of ninety-three matings yielded one hundred and seventy offspring. The distribution of these in the various groups and the average birth weight of the offspring in each group are shown by the following table:

TABLE 2.

	Matings.	Offspring.	Average Birth Weight.
Free male with free female	32	58	81.5 grams
Lead male with free female	34	65	66.3 "
Free male with lead female	27	47	69.3 "

Thus it will be seen that the offspring of lead-poisoned fathers fell, on an average, 15.2 grams below the normal birth weight, and that the offspring of lead-poisoned mothers averaged 12.2 grams below the normal birth weight. That the difference in the latter case is not greater than 12.2 grams is doubtless due to the fact that in most cases no lead was given the female pigs during the nursing period, for we were interested in the rate of growth of the offspring and did not care to introduce the factor of a possible poisoning of the young through the milk. As a result, the administration of lead to the female pigs was necessarily somewhat irregular and some of them conceived at a time when they were comparatively free from the poison. As shown by individual cases, when lead was administered continuously to the female pigs the birth weight was reduced to even a greater degree than when the father was lead poisoned.

In addition to the average birth weight, the number of stillborn offspring and the number dying in the first week after birth were observed as additional points which might indicate a possible injury to the germ plasm. In the table which follows these data are given for the offspring in the various groups:

TABLE 3.

	Offspring.	Stillborn.	Died First Week.
Free male with free female	58	3	2
Lead male with free female	65	3	9
Free male with lead female	47	8	0

It will be noted that there were eight stillborn out of forty-seven offspring of lead females as compared with three stillborn out of fifty-eight offspring of control pigs and that nine out of sixty-five offspring of lead males died during the first week as compared with but two out of fifty-eight control pigs.

The results obtained in certain guinea-pig families by breeding the mother alternately to lead-poisoned and to normal males may also be conveniently shown in tabular form.

TABLE 4.

Offspring of Normal Female No. 36.

By lead male No. 11	69 grams. 65 "
By free male No. 9	91 grams. 90 "

It will be noted that the difference between the average birth weights in these two litters is 23.5 grams.

TABLE 5.

Offspring of Normal Female No. 57.

By lead male No. 50	54 grams.
	47 "
	40 "
By free male No. 9	79 grams.
	79 "

It is evident that the difference of thirty-two grams between the average birth weights in these two litters is much greater than can be accounted for by the difference in the number of offspring in the two cases. Of the three dwarfed descendants of the lead father the smallest died on the fourth day, but the other two grew to maturity in spite of the fact that they were but little more than half normal size at birth.

TABLE 6.

Offspring of Normal Female No. 42.

By lead male No. 11	51 grams.
	37 "
By free male No. 9	105 grams.
	101 "
By free male No. 9	75 grams.
	70 "
	62 "
	52 "

In the third litter of four pigs with a normal father, the smallest weighed more than the larger of two pigs in the litter produced by a lead-poisoned male.

TABLE 7.

Offspring of Normal Female No. 29.

By lead male No. 26	70 grams.
By lead male No. 50	57 grams. 48 " 46 "
By free male No. 10	90 grams. 75 " 75 "

The last two litters produced by normal female No. 29 are especially good for comparison since the number of offspring was the same in each. For the same reason Table No. 8 showing the birth weights of the offspring of Free Female Guinea-pig No. 20 is included here. From this pig there were four litters, two of two each, and two of four each. Thus differences in birth weights due to the varying numbers in successive litters could be eliminated.

TABLE 8.

Offspring of Normal Female No. 20.

By lead male No. 17. (Had received lead for but two weeks; practically a normal male.)	65 grams.
	60 "
By lead male No. 11	43 grams.
	41 "
By free male No. 9	77 grams.
	76 "
	71 "
	66 "
By lead male No. 50	59 grains.
	49 "
	46 "
	38 "

It must not be supposed that all the results obtained were as uniformly consistent as in the five groups presented in Tables 4 to 8. If such had been the case the summaries presented in Tables 2 and 3 would have been even more conclusive, but they include all of the pigs born during the course of this experiment and therefore contain such irregular cases as appear in the following tables:

TABLE 9.

Offspring of Normal Female No. 15.

By normal male No. 10.	87 grams.
By lead male No. 26.	76 grams.
	70 “
By lead male No. 26	75 grams.
	55 “
	53 “
By lead male No. 26.	*112* grams.
	95 “

TABLE 10.

Offspring of Normal Female No. 19.

By a normal male	85 grams.
By lead male No. 17.	84 grams.
	80 “
By normal male No. 9	70 grams.
	66 “
	63 “

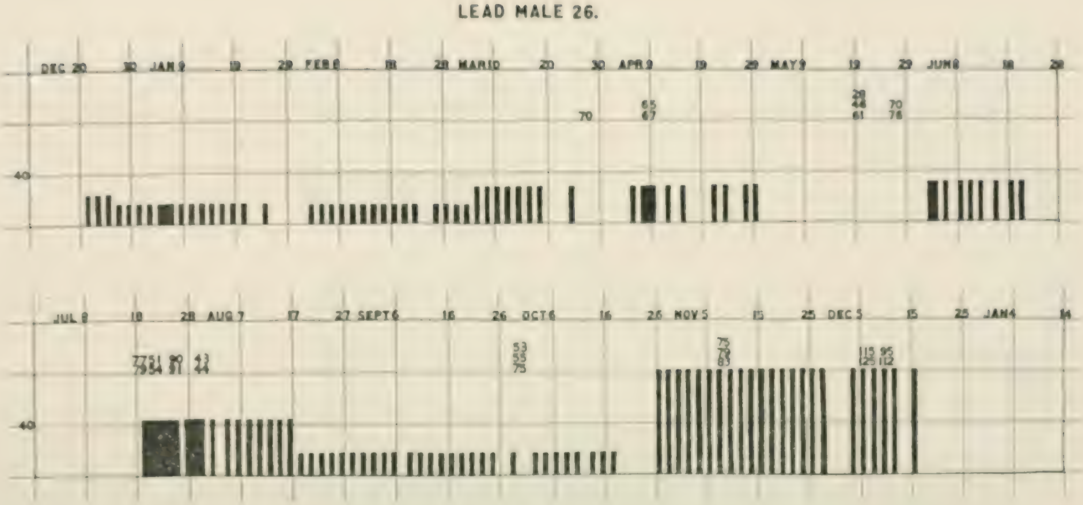

Fig. 3.

Graphic representation of the relationship between lead dosage and weight of offspring for Lead Male Guinea pig No. 26. The dosage of lead is in milligrams and the birth weights of all offspring are indicated in grams and are set back to the probable date of conception.

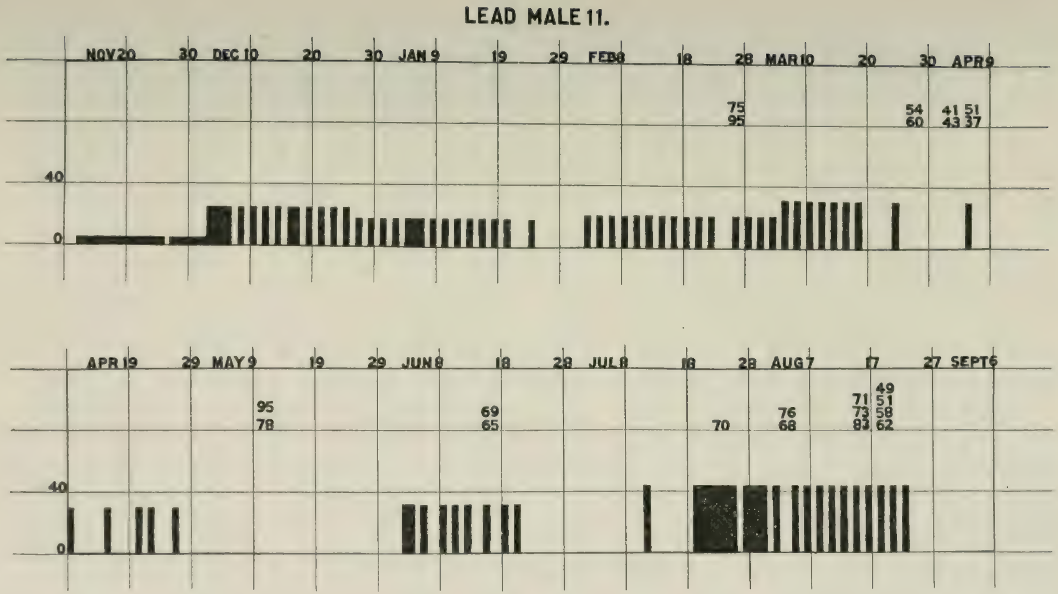

FIG. 4.

Graphic representation of the relationship between lead dosage and weight of offspring for Lead Male Guinea-pig No. 11. The dosage of lead is in milligrams and the birth weights of all offspring are indicated in grams and are set back to the probable date of conception.

The extent to which such irregular results appeared can best be shown by presenting graphically the entire history of some of the lead-poisoned males. This is done in Figures 3 and 4, in which the complete data as to lead dosage and birth weights of offspring are presented for Lead Males Number 26 and 11 respectively. The daily dosage in milligrams of commercial white lead is indicated by the solid black columns, and the birth weights of the offspring are indicated in figures, which are set back so as to appear at the probable date of conception instead of the date of birth. Recalling that the average birth weight of normal pigs in our series was 81.2 grams, it is noteworthy how many of these weights fall far below that standard, but an interesting exception is found in the last two litters produced by Lead Male No. 26, which were conceived at a time when he was receiving a relatively heavy dosage of lead.

Discussion of results of breeding experiments. — In general, no marked reduction in fertility is shown by the results of breeding lead-poisoned guinea-pigs. Notwithstanding the fact that in several instances lead-poisoned males failed for three or four months to impregnate any of the females with which they were running, the average number of offspring per mating in this group is practically the same as in the group of normal pigs. Only one of the lead-poisoned males proved absolutely sterile. Lead Male No. 44, weighing five hundred grams when lead was first administered, failed to impregnate any of the five adult females with which he was caged for eight months. During this period there was no apparent loss of sexual desire or sexual activity. All of these females proved fertile when a normal male was substituted for No. 44. Likewise, in the female there was no loss of fertility.

The birth weight of the offspring proved to be the factor which was most consistently affected by chronic lead poisoning in the parents. In normal pigs the weight of the young at birth is varied to some extent by the age of the mother, but more so by the number of young in each litter and by the individual habit of the female, since some animals, regardless of the male parent, always produce young much below the average in weight. The effect of the first two of these factors has been overcome by the comparatively large number of observations from which our averages were obtained, while the method of breeding alternately to lead-poisoned and to normal males serves to control the intrinsic variations in the females. With these precautions, a reduction in the weight of the offspring of lead-poisoned males of 15.2 grams, equal to 18.6 per cent of the average birth weight of normal pigs, can be attributed only to the blastophthoric effect of the lead.

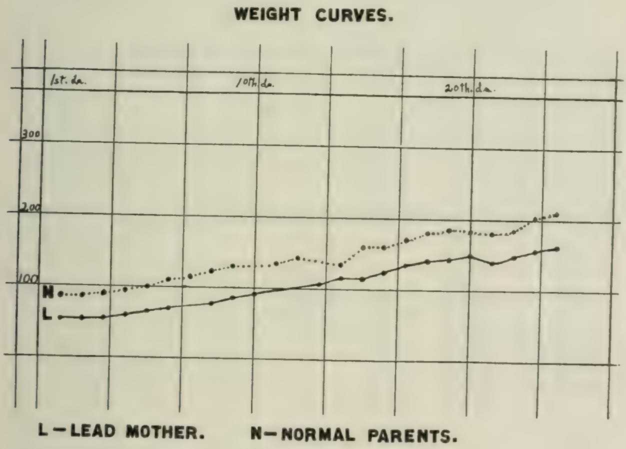

Fig. 5.

The weight curves of two newborn guinea-pigs. The one from a normal mother is indicated by a dotted line, the one from a lead-poisoned mother by a solid line. The lead offspring remains permanently underweight.

Upon the maternal side, the reduction in birth weight does not lend itself as a proof of blastophthoria. However, it is a very significant fact that the offspring of female guinea-pigs, chronically poisoned with lead in such a slight degree that they did not themselves show any ill effects, weighed on the average 12.2 grams, equal to 14.9 per cent less at birth than did the offspring of normal pigs.

Those offspring of a lead-poisoned parent which are decidedly below the average weight at birth remain permanently underweight as compared with normal pigs of the same age. In Figure 5 are shown the weight curves of two young growing pigs, one with normal parents and one with a lead-poisoned mother. Although the latter more than doubled its birth weight in twenty-four days, at the end of that period it was fifty grams smaller than the guinea-pig born of normal parents.

Stillbirths are not common among normal guinea-pigs, nor were we able to show that lead intoxication of the male parent results in any increase in the number of stillborn offspring. However, the increased mortality of this group in the first week of life makes it seem very probable that an intoxication of a more severe degree would result in stillbirths among the offspring of lead fathers. When the mother is lead poisoned, stillbirths are numerous. The following table of the offspring of Lead Female No. 25 will illustrate this point:

TABLE II.

Offspring of Lead Female No. 25.

By free male No. 10	40 grams	Stillborn.
	18 "	"
By free male No. 10	107 grams	Living (Lead was withheld from the mother for 10 weeks, but was again administered during the last 3 weeks of pregnancy.)
By free male No. 10	54 grams	Stillborn.
	45 "	"
	41 "	"

The stillborn offspring of a lead mother are usually premature and often show by maceration of the skin that they have been dead for some time before expulsion.

Next to reduced birth weight, the high mortality during the first few days after birth was the most striking change shown by the offspring of lead males. As already noted in Table 3, from a total of one hundred and seventy pigs born in the course of this experiment eleven died during the first week after birth. Of these eleven, nine are found in the group of sixty-five offspring of lead males. While it is true that these guinea-pigs were underweight at birth, they were not premature but were well proportioned, had their eyes open and were quite active. Nor was their small size at birth the sole determining factor in causing their early death, for we have grown to maturity many of these dwarfed pigs weighing, for instance, 43, 44.5, 46 (3), 47, 48, and 49 grams at birth. Rather must it be considered that the small size at birth and the lessened vitality of the offspring of lead males are both manifestations of an injury to the male germ plasm. When both of these factors are present in a well-marked degree the offspring of such parents usually die in the first week.

In only two instances were malformations observed in the first filial generation. Two pigs showed a slight malformation of the upper jaw with deformed teeth. Occurring in so few instances, this malformation may have been due to some nutritional disturbance, and not to blastophthoria. However, special attention will be paid to the appearance of this or any other malformation in the second filial generation, upon which report cannot as yet be made.

A recovery of the germ plasm following the toxic injury is indicated by some of our results. On the charts showing the birth weights of all of the progeny of Lead Males Nos. 11 and 26 (Figs. 4 and 3) it will be noted that there is some tendency for offspring of more nearly average birth weight to be produced shortly after the intermissions in the administration of lead. Also in the case of Lead Female No. 25 (Table 11) the only living offspring, an active pig of more than average weight at birth, was conceived during a period when the administration of lead was interrupted. If these are in reality examples of an apparent recovery of the germ plasm following the withdrawal of the injurious agent it seems probable that the blastophthoric effect is exercised upon that portion of the germ plasm which is in process of maturation and not upon the reservoir of germ plasm in the germinal epithelium. This point will require further investigation.

Conclusions. — From the entire series of matings the following conclusions can be drawn:

1. In chronic lead poisoning in guinea-pigs there is a definite blastophthoric effect. This can best be demonstrated upon the male germ plasm, in which case the blastophthoria manifests itself in some instances by sterility without loss of sexual activity, by a reduction of approximately twenty per cent in the average birth weight, by an increased number of deaths in the first week of life, and by a general retardation in development such that the offspring of a lead-poisoned male remain permanently underweight.

2. The offspring of a lead-poisoned female are underweight at birth and are very frequently stillborn. The number of stillbirths is out of proportion to the degree of intoxication of the mother and points either to a special susceptibility of the embryonic tissues to lead or to a blastophthoric effect upon the female germ plasm.

3. From the apparent recovery of reproductive power some time after stopping the administration of lead it seems that the deleterious effect must be suffered especially by that portion of the germ plasm which is undergoing maturation and not by that which is stored as undeveloped germinal epithelium.

REFERENCES.

1. Paul, Constantin. Archives Générales de Médecine, i, 1860, 513.

2. Oliver, Sir Thomas. A lecture on lead poisoning and the race. Brit. M. J., Lond., 1911, i, 1096–1098.

3. Reid, G. Report of the Department Commission on the dangers attendant on the use of lead, ii. Quoted by Oliver.[2]

4. Chyzzer, A. Des Intoxications per le Plomb se présentant dans le Céramique en Hongrie. Chir. Presse, Budapest, 1908, xliv, 906.

5. Thompson. The Occupational Diseases, 234. Appleton & Co., 1914.

6. Rudeaux. La Clinique, Jan. 21, 1910. Quoted by Thompson.

7. Legge and Goadby. Lead Poisoning and Lead Absorption. Longmans and Co., 1912, 35.

8. Glibert, D. J. Le Saturnisme Expérimental. Extrait des Rapports Annuels de l'Inspection du Travail. Bruxelles, 1906. Quoted by Legge and Goadby.[7]

9. Cole, L. J., and Bachhuber, L. J. Proc. of the Soc. for Exp. Biol. and Med., xii, 24.

THE JOURNAL OF MEDICAL RESEARCH, VOL. XXXIII., No. 2, November, 1915.

Two Additional Cases of Miliary Tuberculosis of the Placenta with Clinically Latent Tuberculosis of the Mother

CARL VERNON WELLER, M.D.
Instructor in Pathology, University of Michigan
ANN ARBOR, MICH.

Reprinted from the Archives of Internal Medicine
April, 1916, Vol. XVII, pp. 509-515

CHICAGO
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
1916

TWO ADDITIONAL CASES OF MILIARY TUBERCULOSIS OF THE PLACENTA WITH CLINICALLY LATENT TUBERCULOSIS OF THE MOTHER *

CARL VERNON WELLER, M.D.
Instructor in Pathology, University of Michigan
ANN ARBOR, MICH.

The two cases of placental tuberculosis which form the subject of this report are of unusual interest, for in each the disease was so slightly active as to be unrecognized clinically in the mother, but was found in the course of the routine microscopical examination of the placenta. In one instance no history suggestive of tuberculosis could be elicited and the disease, apparently incipient during pregnancy, has become latent since the birth of the child. This case, therefore, is similar to the one reported from this laboratory in 1913 by Dr. Warthin,[1] in connection with which he at that time called attention to the increased importance of the sociologic and eugenic aspects of the transmission of tuberculosis from parent to child, provided that it can be shown that in women who have incipient or clinically unrecognizable tuberculosis the bacilli may enter the blood stream and cause a miliary tuberculosis of the placenta or congenital infection of the fetus.

The second case to be reported is in some respects even more unique. In this instance, also, the maternal tuberculosis was clinically unrecognizable at the time of admission to the hospital and was found only through the discovery of miliary tubercles in the course of the routine examination of the placenta. This patient, however, had wilfully falsified in regard to her history in order to conceal an earlier diagnosis of tuberculosis. This she admitted when she was told of the finding of placental tuberculosis. Unlike the first case and the one recently reported by Dr. Warthin, this woman's tuberculosis became more active after the birth of the child and she returned to the hospital with unmistakable clinical signs of pulmonary tuberculosis.

Without including here a review of the literature, attention is called to the fact that the reported cases of placental tuberculosis may be arranged in three groups:

1. Cases in which the mother was known to be tuberculous and in which, as a result of this knowledge, the placenta was given intensive

---

* From the Pathological Laboratory of the University of Michigan.

[1] Warthin, A. S.: Miliary Tuberculosis of the Placenta, Jour. Am. Med Assn., 1913, lxi, 1951.

study and found to exhibit the characteristic lesions of tuberculosis, either with or without a demonstration of the bacilli.

2. Cases in which the mother was known to be tuberculous and in which the presence of tubercle bacilli in the placenta or the fetal blood was demonstrated by staining methods or by animal inoculation without the recognition of the lesions of tuberculosis in the placenta. One must believe that in many of these cases the failure to find lesions was due either to unfamiliarity with the somewhat varied microscopical picture of placental tuberculosis, or to the fact that the amount of placental tissue examined in section under the microscope was such a small proportion of the total organ that characteristic lesions were not included.

3. Cases in which the maternal tuberculosis was clinically unrecognizable and in which characteristic histopathologic lesions of tuberculosis were found in the routine examination of the placentas. In this group fall the two cases forming the subject of this report, the only other case in the group being the one reported by Dr. Warthin, to which reference has been made.

That three such cases should be found in one laboratory and within the space of three years is strong additional argument, not alone for the belief that the maternal transmission of tuberculosis is much more common than is ordinarily taught, but also for the little recognized fact that a "subclinical" tuberculosis may be so influenced by pregnancy that bacilli may enter the blood stream and produce placental or fetal miliary tuberculosis.

REPORT OF CASES

Summaries of the histories of the two cases here reported follow:

Case 1.—Miss K., aged 21, entered the maternity ward of the University Hospital, service of Dr. Reuben Peterson, April 23, 1914. The patient was then in about the eighth month of pregnancy. There was no history of tuberculosis in her family, father, mother and eight brothers and sisters being alive and well. One sister died in childbirth. On physical examination by Dr. Seeley the patient was found to be of slight build but fairly well nourished. No signs of any pulmonary lesion were discovered and the examination of the heart was likewise negative. The findings in the routine ante partum obstetrical examination do not concern us here. The Wassermann reaction was reported negative by one serologist and positive (one plus) by another. Blood and urinary findings were negative.

June 11, the patient was delivered by Dr. Bartholomew of an apparently healthy female child. The puerperium was uneventful and the patient returned to her home June 27. The child was left at the University Hospital until July 16. It was then 35 days old, had gained 550 gm., and was apparently normal in all respects.

The placenta from this birth was placed in formol after being securely tagged with the name of the mother. It was sent to the pathological laboratory and in the course of the routine microscopical examination miliary tubercles were found. These lesions will be described later.

In October, 1915, the family physician of this patient, replying to an inquiry addressed to him by Dr. Loomis, said that both mother and child were under observation, were apparently well and had given no evidence of tuberculosis at any time.

Case 2.—Mrs. C., aged 27, was admitted to the obstetrical wards of the University Hospital, service of Dr. Peterson, Jan. 28, 1914. She was then in the ninth month of pregnancy. The patient denied any family history of tuberculosis, saying that her father, mother, three brothers and two sisters were living and well. Two sisters died in childhood. Concerning her personal history she said that she had never been strong until the past few years, but that she had made a good recovery from measles and scarlet fever in childhood and also from "congestion of lungs and bowels" five years previously. The patient was married nine years before and had one child, aged 7. There had been no other pregnancies.

The history of the present pregnancy presented nothing unusual. There had been considerable nausea and vomiting in the second and third months, but little afterward. No eye symptoms or dizziness, no swelling of ankles, no headache had occurred.

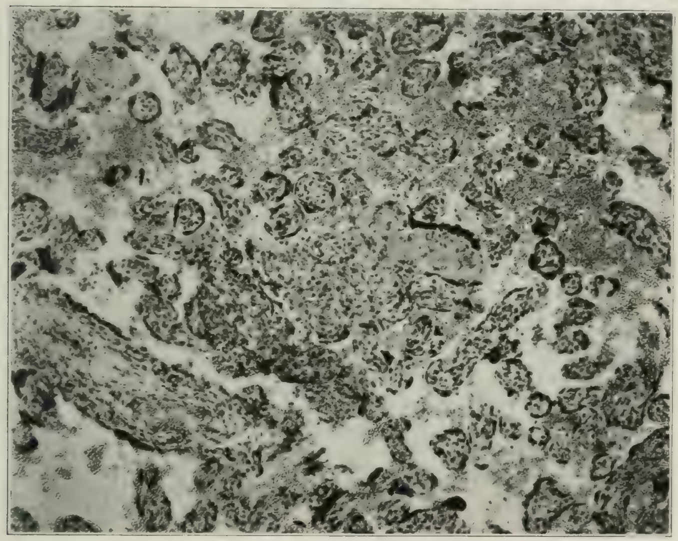

Fig. 1.—Miliary tuberculosis of the placenta. Clinically latent tuberculosis of the mother. In the center of the field an intervillous epithelioid tubercle.

On physical examination, made by Dr. Loomis Jan. 30, 1914, the patient was found to be of a rather large frame, with musculature and panniculus good. Face pale, but conjunctivae and lips of good color. Eyes reacted normally to light and accommodation. Neck, mouth and throat were negative. The thorax presented marked infra- and supraclavicular fossae and was found to be somewhat larger, and to move more freely on the left than on the right side. The lung borders had a wide excursion. Resonance was normal. The breath sounds were likewise normal except for occasional piping râles, and the voice sounds were generally, but uniformly, increased. It was noted that the patient had some cough, and accordingly fine crackling râles were carefully sought for but were not heard. Auscultation and percussion of the back gave only negative findings.

The routine antepartum examination of breasts, abdomen and pelvis need not be detailed. There was no indication that the confinement would be otherwise than normal. Such proved to be the case, and Mrs. C. was delivered rather precipitately Feb. 4, 1914. The child was an apparently healthy male weighing 7 pounds, 4 ounces. The puerperium was normal throughout and the history of the child was uneventful during the fourteen days that it remained in the hospital. At the expiration of this period the mother took the child to her home in a distant part of the state.

The placenta from this birth was placed in 10 per cent. formaldehyd solution at once and delivered to the pathological laboratory March 8, 1914. In the routine microscopical examination of this placenta there was found a group of four or five miliary tubercles. The microscopical findings will be described in greater detail later.

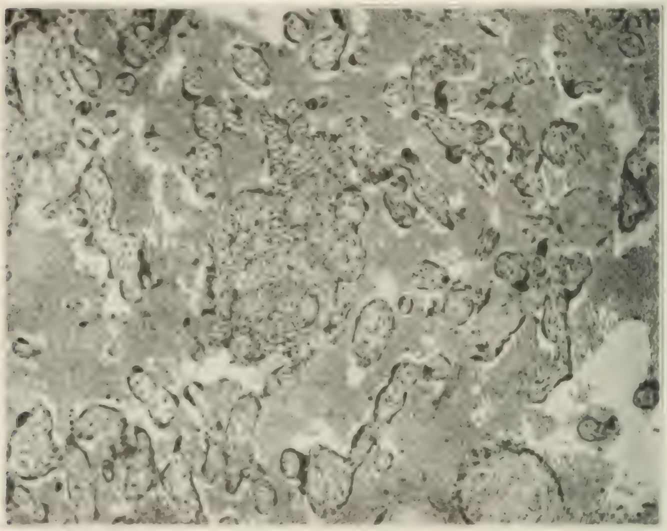

Fig. 2.—Miliary tuberculosis of the placenta, Case 2. Pulmonary lesion unrecognizable during pregnancy, but becoming active after birth of child. An intervillous epithelioid and giant-cell miliary tubercle.

In January, 1917, letters of inquiry were sent to Mrs. C. and to her home physician asking for additional information as to a possible history of tuberculosis (although the patient had stated that there was no history of tuberculosis in the family) and also in regard to the condition of both mother and child. The reply of the mother was especially interesting, throwing, as it did, much light on the subsequent history of the case and revealing an altogether too common attitude on the part of the patient. Mrs. C.'s letter follows in part:

"... I am very glad to be able to send you a favorable report; also glad to know you are interested enough in us to write and inquire. Baby is strong and well and has never been sick enough to call a doctor . . .

"As to my own health, I am well and strong as can be. I have had perfect health ever since I left the hospital. I understand that Dr. Peterson wrote to our doctor here, saying that at the time of the baby's birth you found signs of tuberculosis. I am not at all surprised as I have been told before that I had tuberculosis but I did not believe it, so thought I would not speak of it and *let you find it if you could*. I lay our good health all to fresh air, for we are fresh air fiends . . ."

The patient's home physician kindly wrote under date of Jan. 19, 1915, saying that Mrs. C. had a history of tuberculosis dating back some eight or ten years. He had not had an opportunity to examine mother or child since her confinement, but as far as he could learn they were apparently well. Five months later (June 30, 1915) her physician again wrote, saying that Mrs. C. was losing weight rapidly and apparently doing badly, although no active pulmonary focus was discovered. The baby remained in "excellent condition." Because of this information the patient was advised to return for examination, which she did July 26, 1915, entering as an outpatient, the service of Dr. A. W. Hewlett, through whose kindness the notes taken at that time were placed at my disposal. The patient then disclosed her earlier history of pulmonary tuberculosis. She said that she had had pneumonia in the right lung six years previously, after which she did not recover strength and was told that she had tuberculosis. Accordingly she went West for three years, but returned apparently perfectly well.

In the seventeen months which had elapsed since the birth of her child, the patient had been well, except for some cough and sputum, until the beginning of the summer, when she began to grow weak and tired and to raise more sputum. The following April she had pain in the right upper chest, at some times dull and radiating to the scapular region, and at other times knife-like in character, keeping her awake at night. She had been taking her own temperature at 4 p. m. each day but had had no fever except for a period of about one month, when she had noted an afternoon temperature 2 to 3 degrees above normal. During that month she was very tired so that she had to go to bed most of the time, but more recently she had felt stronger. There had been a loss of weight of 20 pounds in the previous six months.

In examining the patient at this admission, Dr. Hewlett found increased fremitus in the right scapular region and beneath the inner end of the right clavicle. Sharp crackling râles, brought out by coughing, were occasionally heard in the interscapular region. A diagnosis of pulmonary tuberculosis was made.

The lesions discovered microscopically in the placentas of these two patients are in every respect characteristic and there can be no doubt that they are miliary tubercles. Without a detailed discussion of the histopathology of placental tuberculosis (which may be found in the papers of Schmorl and Geipel[2] and Warthin[3]), attention is called to the fact that the differential diagnosis of placental tubercles presents but few difficulties if the lesions are present in at least moderate numbers and have not reached a stage of advanced healing. This point has been emphasized by Warthin,[1] and he has shown that even when the tubercles have advanced to a healing stage the two other things which need to be considered in differentiation are essentially unlike them. In small localized areas of *syphilitic chorionitis* the process involves only the stroma of the villi and the villi are not fused into a solid fibroblastic or fibroid mass. In the small *healing infarct* the villi may be fused, but there is no fibroblastic formation, or only the slightest, between them. In the *healing tubercle*, on the other hand, if villi are fused in the mass, there is an abundant intervillous epithelioid or fibroblastic proliferation.

---

[2] Schmorl and Geipel: München. med. Wchnschr., 1904, li, 1676.

[3] Warthin, A. S.: Jour. Infect. Dis., 1907, iv, 347.

MICROSCOPICAL FINDINGS

The original sections made in the routine examination of *Case 1* each showed four or five young and active miliary tubercles. Examination of other sections has shown that the distribution varies somewhat, but no section examined from this case has failed to disclose at least one tubercle. These tubercles are practically all in about the same stage, showing an active epithelioid proliferation without caseation, although some of the larger ones reveal a slight karyorrhexis and diffusion of chromatin. Giant cell formation was not noted. In regard to location, a large majority of the tubercles are intervillous, often involving within the mass four or five villi the outlines of which may still be made out around the periphery of the tubercle. Fewer intravillous tubercles are found and these correspond in their young epithelioid character to those just described. Earlier stages were not found, so that the bacilli must have been given off some time before delivery, and most of them at about the same time.

The original section from which the diagnosis of placental tuberculosis was made in *Case 2* showed a group of four or five intervillous miliary tubercles which were epithelioid in character. Study of a large number of sections from this case shows the total number of tubercles to be much smaller than in Case 1, many sections containing none, and but rarely more than one to a section being found. Although various stages are present, in general these tubercles are somewhat older than those of Case 1. None, however, show healing, but typical Langhans' giant cells are frequently seen, and in some instances there is an early fibroblastic proliferation. As in the first case, intervillous tubercles greatly predominate over those of other locations.

It is to be regretted that it is technically impossible to demonstrate tubercle bacilli in the lesions in these placentas. They were both intensely fixed in formol, which always makes the differential staining of the tubercle bacillus very difficult and often impossible. We are not alone in this experience as it is mentioned in various works on microscopic technic and constitutes one of the many objections to the routine use of formol as a fixing agent. We believe, however, that our inability to demonstrate the bacilli does not in the least detract from the value of these cases, for the lesions are absolutely characteristic; they differ in no respect from similar lesions in other cases in which the bacilli have been demonstrated in large numbers; and in one of the two cases here presented, the diagnosis of tuberculosis has been supported in an unusual way by the subsequent development in the mother of an active pulmonary process.

As far as can be ascertained, there has been no evidence of tuberculosis in either of the children from these births. Whether this is due to the fact that the bacilli were of relative slight virulence, or that they passed the placenta in too small numbers to determine a clinically recognizable infection, or whether the fetal tissues offered more than ordinary resistance, can only be conjectured.

SUMMARY

The two cases of placental tuberculosis here presented were discovered in the routine microscopical examination of the placentas. The mothers did not have clinically recognizable lesions at the time of delivery, but in one case an active pulmonary tuberculosis later developed. The other case became latent after the birth of the child. These cases are additional proof of the fact that even an incipient and unrecognizable tuberculosis may be so influenced by pregnancy as to cause a placental, and therefore potentially a fetal, miliary tuberculosis.

My thanks are due Dr. A. S. Warthin, who made the original diagnosis of placental tuberculosis in these cases, for placing the material at my disposal; to Dr. Reuben Peterson and Dr. A. W. Hewlett for the use of the records of their respective departments; and to Dr. F. L. Loomis of the Department of Obstetrics and Gynecology for his assistance in following up the after-history of the cases.

The Coincidence of Latent Syphilis and Diabetes

BY

ALDRED SCOTT WARTHIN, Ph.D., M.D.
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR

AND

MISS UNITY F. WILSON
RESEARCH ASSISTANT IN PATHOLOGY

FROM THE
AMERICAN JOURNAL OF THE MEDICAL SCIENCES
August, 1916, No. 2, vol. clii, p. 157

Extracted from the American Journal of the Medical Sciences,
August, 1916, No. 2, vol. clii, p. 157.

THE COINCIDENCE OF LATENT SYPHILIS AND DIABETES.

By Aldred Scott Warthin, Ph.D., M.D.,
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR,
AND
Miss Unity F. Wilson,
RESEARCH ASSISTANT IN PATHOLOGY.

(From the Pathological Laboratory of the University of Michigan.

Very little attention has been given in the literature to a possible relationship between syphilis and diabetes mellitus. Most writers on internal medicine deny any etiological relationship between the two conditions, or do not even mention such a possibility; while a small minority think that syphilis may only rarely be a cause of diabetes or glycosuria. We may here quote Futcher's article on diabetes mellitus in the last edition of Osler's *System*: "In occasional instances diabetes may be traced to a syphilitic infection. Feinberg reported three cases of diabetes and one of glycosuria which he attributed to a syphilitic infection. When syphilis plays a part, the lesion is most probably a local one, and most likely to be situated in the region of the medulla or pituitary gland. Nutritional changes in the brain and pancreas from syphilitic arterial disease must be considered as a possible cause."

On the very next page of Futcher's article there is an apparent contradiction of the above statement as to the occasional relationship of syphilitic infection and diabetes, in the following: "Observers agree in the comparative frequency of glycosuria, or a mild diabetes in *general paresis*. Bond reports having found it in 10 per cent., and Strauss in 9 per cent. of their cases. Glycosuria is an occasional accompaniment of *tabes dorsalis* and *multiple sclerosis*." It is evident that if 9 to 10 per cent. of paretics show glycosuria or a mild diabetes, the relationship between syphilis and glycosuria is not an occasional one. During the last several years there have appeared evidences, more or less vague, that the attention of clinicians was slowly being directed to a more decided appreciation of relationship between the two diseases. The occurrence of positive Wassermanns in some diabetics, apparent improvement following the therapeutic use of mercury or salvarsan, the association of glycosuria in children with congenital syphilis, and the same condition in adults with paresis, tabes and other syphilitic affections are reported in recent literature more or less incidentally. At the meeting of the American Medical Association in San Francisco, I took the opportunity of asking clinicians from all parts of the country as to their experience with coincident diabetes and syphilis, and was surprised to find that the majority of those interrogated thought the coincidence not a rare one. On the other hand, other clinicians with large experience thought the combination of the two conditions to be so infrequent as to be clinically negligible.

Since 1907 there have occurred in the autopsy service of the pathological laboratory of the University of Michigan six autopsies on cases of diabetes mellitus. It is of special interest to record that all six of these cases presented histological changes of syphilis, and that in four of them the spirochetes have been demonstrated in the myocardium, and in one of these cases also found in the pancreatic lesions. The case history of these six cases are briefly as follows:

Case I.—Mr. D. F., aged sixty-two years; American; farmer by occupation. Transferred from surgical clinic to medical February 27, 1907, for diabetes mellitus, gangrene of both feet, and erysipelas of face. No history of venereal disease obtainable. One sister died of diabetes. No other symptoms of diabetes. *Urine*: specific gravity 1030 to 1033; showed marked reduction of Fehling's; 3.2 per cent. Lohnstein; polariscope, 3.3 per cent.; positive acetone. On March 4, patient gradually became comatose, with marked odor of acetone on breath. Died in coma on the next day.

Pathological Findings. The autopsy findings were: diabetes mellitus; emphysematous gangrene; atrophy, fatty infiltration, and chronic interstitial inflammation of pancreas; syphilitic myocarditis and aortitis; orchitis syphilitica fibrosa; atrophy and chronic passive congestion of all organs.

The microscopic examination showed fibroid patches in myocardium, coronary sclerosis, and small perivascular infiltrations throughout the heart wall. The aorta wall showed marked atherosclerosis, with areas of mononuclear infiltration around the vasa vasorum, particularly around the veins of the outer portion of the media and in the adventitia (syphilitic aortitis). The testes showed an old syphilitic orchitis fibrosa. The changes in the pancreas will be described below. This material has not yet been examined for spirochetes.

Case II.—Mrs. M. M., aged forty-five years; American; housewife. Admitted to the University Hospital May 25, 1911. Five months before the patient had first noticed increased thirst and pruritus vulvæ, with increasing general weakness. Mother died at fifty-four years of diabetes; one of patient's sisters also had diabetes; no history of venereal disease; has had two miscarriages; four children living and well. On May 26 developed air hunger and strong odor of acetone. *Urine:* specific gravity, 1026; positive tests for acetone and diacetic acid; glucose, 24.7 gms. per day. Died in coma on May 31.

Pathological Findings. Diabetes mellitus; atrophy and chronic inflammation of pancreas; chronic fibroid myocarditis; syphilitic aortitis; arteriosclerosis; acute parenchymatous nephritis; chronic passive congestion and atrophy of all organs; old syphilis.

The microscopic study confirmed the diagnosis of syphilitic myocarditis, aortitis, and pancreatitis; material not examined for spirochetes. Pancreatic changes will be described below.

CASE III.—Mr. J. K., aged thirty-eight years; foreigner; laborer. Admitted October 14, 1913. A few weeks previously began to have excessive thirst and to pass large quantities of water. Lost thirty pounds in four weeks. Has attacks of dyspnea and odor of acetone in breath; became stuporous soon after admission. Admitted gonorrhea; denied syphilis. Died in coma twenty-four hours after admission. *Urine*: specific gravity, 1031; glucose, 154 gms. in twenty-four hours; oxybutyric and acetone tests positive.

Pathological Findings. Diabetes mellitus; chronic interstitial pancreatitis with hyaline fibrosis of islands of Langerhans; fibroid heart; syphilitic aortitis; orchitis fibrosa syphilitica; arteriosclerosis; acute emphysema; passive congestion of all organs.

The microscopic examination showed latent syphilis of heart, aorta, pancreas, and testes. Examination for spirochetes by Levaditi method showed typical spirochetes of syphilis in myocardium, bloodvessel wall in adventitia of aorta and in the pancreas. Pancreatic changes will be described below.

CASE IV.—Mr. F. A., aged forty-eight years; American; mail-carrier. Admitted on December 12, 1913. History of alcoholism, but denied venereal infection. One sister died of diabetes. Entered surgical clinic for suppurating wound of right hand. Complained of thirst and was drowsy. Cellulitis of right hand and arm with beginning gangrene. Developed air-hunger on the next day, followed by coma and rather sudden death. *Urine*: specific gravity, 1022; glucose, 40.25 gms. in twenty-four hours; positive acetone.

Pathological Findings. Diabetes mellitus; chronic pancreatitis with hyaline changes in islands of Langerhans; fat necrosis; infected primary squamous-cell carcinoma of finger with purulent lymphangitis of right arm; septicemia; fibroid heart; aortitis; orchitis fibrosa syphilitica; emphysema; early sclerosis; cloudy swelling of kidney and liver; passive congestion of all organs.

Microscopic examination showed chronic syphilitic myocarditis, aortitis, pancreatitis, and orchitis. Spirochetes of syphilis were found in the myocardium in a loose cellular connective tissue bordering upon a fibroid area.

Case V.—Mr. Le F., aged forty years; French; occupation not given. Admitted March 5, 1914. Presented general anasarca, ascites, dyspnea, drowsiness, cyanosis, and deep ulcers on both legs. Left foot had been amputated above the ankle. Remained under observation until death on January 7, 1915. Clinical symptoms those of uremia. Urine tests do not mention glucose examination. Clinical diagnosis: diabetes mellitus; diabetic gangrene; chronic nephritis: myocardial insufficiency.

Pathological Findings. Diabetes; old syphilis; chronic myocarditis; aortitis; hepatitis; pancreatitis; nephritis; orchitis. Chronic passive congestion and atrophy of all organs. Syphilitic ulcers of leg; old amputation; obesity; decubitus; cholelithiasis.

The microscopic examination showed syphilitic myocarditis, aortitis, pancreatitis, orchitis, and gummatous ulcers of legs. Spirochetes of syphilis were demonstrated in the myocardium by the Levaditi method.

Case VI.—Mr. W. E., aged sixty-six years. Entered as an emergency case on January 1, 1915, in a state of coma, moderate fever, auricular fibrillation, rapid irregular pulse, and a spreading cellulitis over the occipital region. Urine gave marked reaction for sugar and definite test for acetone. Complete examination impossible because of patient's condition. Died in delirium on January 3.

Pathological Findings. Diabetes mellitus; phlegmon of scalp and neck; pyemia; metastatic abscesses in lungs, heart, kidneys, and prostate; chronic prostatitis; chronic pancreatitis, with hypertrophy of some islands of Langerhans; chronic fibroid myocarditis; chronic aortitis; chronic orchitis fibrosa; chronic hypertrophic gastritis; old syphilis.

The microscopic examination showed old syphilis of heart, aorta, pancreas, adrenals, and testes. Spirochetes of syphilis were found in the myocardium by the Levaditi method.

Diagnosis of Syphilis. The diagnosis of syphilis in these six cases of diabetes was made upon histological changes alone in Cases I and II, and in the remaining four cases upon both histological changes and the presence of the Spirocheta pallida in the tissues, as shown by the Levaditi method. The material of cases I and II has not yet been studied by the Levaditi method, because of our inability to give the necessary time required for such a research. In Cases III, IV, V and VI the spirochetes were found in the myocardium, and in Case III also in the pancreas, this being the only case in which this organ was examined by the Levaditi method. In Case VI alone were the spirochetes found in large numbers. In all six of the cases the histological changes of chronic fibroid myocarditis and of chronic aortitis of the type always associated with chronic syphilitic infection were present. The microscopic pictures presented by both these conditions are characteristic of syphilis, and would be sufficient in themselves to warrant a diagnosis of syphilis without the corroborating support of the other changes present and the demonstration of the spirochetes. All five of the males showed a typical orchitis fibrosa syphilitica.

Pancreatic Changes. When the pancreas of each of the six cases was given a more detailed study than that made for the autopsy report it was found that the pathological changes were essentially the same in all, but varying in degree. Briefly, these changes may be classified as follows:

1. Atrophy with fatty infiltration (fatty atrophy), involving particularly the tail and body of the organ.

2. Increase of stroma, both inter- and intralobular, particularly marked about the ducts, and extending along the intralobular ducts between the acini and presenting the picture of a chronic interstitial inflammation is shown in all six cases. This is also most marked in the splenic end and body of the organ. The increase of stroma is not uniform but patchy. Normal lobules are side by side with lobules showing a marked fibrosis; and many sections from different blocks may show no increase of stroma at all. Large areas, particularly in the head, appear normal. The lobules showing the increase of stroma are smaller than normal, and contain adipose tissue cells. Occasionally completely fibroid areas are found in the more severe cases.

3. Inflammatory infiltrations, usually small in size, were found in every case, both in the interlobular connective tissue and within the lobules. The cells are almost wholly mononuclears, small and large lymphocytes, and plasma cells. Polynuclears and eosinophiles are rare. The seat of the infiltration is always in a loose, semifluid, proliferating connective tissue, resembling edematous connective tissue, and containing epithelioid fibroblastic cells. These areas are precisely like those in the myocardium containing colonies of spirochetes. In such active inflammatory areas were the spirochetes found in Case III.

4. Changes in the islands of Langerhans were present in all six cases. In all, the islands are undoubtedly greatly diminished in number; in two cases only a few islands remained. Particularly in the tail of the organ is the total or nearly total disappearance of the islands notable. In two cases the remaining islands showed a marked hyaline fibrosis. Opie's hyaline degeneration of the cells of the islands was not seen in any case. The islands are destroyed by a connective-tissue proliferation which soon becomes fibroid and hyaline. A number of hypertrophic islands were seen in one case. No inflammatory infiltrations were found about the islands. It is clear that the destroyed islands are replaced by

irregular masses of fibrous tissue showing no remains of the island structure.

5. The acini in all six cases also showed marked changes. In many lobules atrophic acini are present, particularly in those showing marked fibrosis. The majority, however, are larger than normal, this increase in size being very marked in many lobules. The nuclei are larger and the protoplasm shows a marked increase of zymogen granules. Occasionally acini with hyaline protoplasm staining deep red with eosin are found.

6. Numerous structures looking like newly formed islands are found in the areas showing most marked fibrosis and inflammation. At first glance they were interpreted as such. Minute study showed them to be new-formed lobules of acini arising from the ducts. Their origin from the epithelium of the latter can be easily demonstrated. In some cases they have been seen developing inside large dilated ducts. In their earlier stages they very much resemble the islands of Langerhans, because of the small size of their cells, collapsed lumina, and deeply staining nuclei; but centro-acinar cells are found within the undeveloped lumen of the acinus, and they have not the vascular arrangement of the islands. All stages can be traced between these newly formed lobules and large adenoma-like structures with dilated lumina containing centro-acinar cells. They undoubtedly represent regenerative attempts, a new formation of acini from the duct epithelium. In these six cases I have found no positive evidence of any new formation of islands. In one case (Case VI) very large islands were found and were interpreted as hypertrophic.

6. The bloodvessels show in all cases varying degrees of sclerosis.

7. The ducts are often dilated and show thickened walls. Cystic ducts are present in every case, and are probably retention cysts of intralobular ducts due to the fibrosis. In one of these papilliferous growths were seen.

The question that at once arises is: Are these pancreatic changes the result of syphilis, and are they responsible for the diabetes? The very frequent association with diabetes of chronic interstitial pancreatitis, particularly the interacinar (intralobular) type, has been shown by many writers; and this form of pancreatic lesion is generally regarded today as the most common and important pathological finding in this disease. According to Opie[1] "Chronic interacinar (intralobular) pancreatitis which implicates the islands of Langerhans is in almost all cases accompanied by glycosuria." As to the etiology of the interacinar form of pancreatitis, Opie gives *alcohol* and *arteriosclerosis* as the only definite causes, saying that "in some cases the etiology of interacinar pancreatitis is obscure." He does not even mention the possibility of syphilis

[1] Osler's System.

as an etiological factor in pancreatitis. In his paragraph on "Syphilis of the Pancreas," he does not mention the occurrence of pancreatitis in acquired syphilis, but says that the pancreas is rarely the seat of gummata occurring as the result of acquired syphilis, and that there are no data with reference to the symptoms or diagnosis of syphilis of the pancreas. In the article on Syphilis by Osler and Churchman[2] the statement is made that the pancreas is only rarely attacked, and that Herxheimer gives only three cases of pancreatic gumma from the literature. Here again the only criterion taken for the presence of a syphilitic lesion is the old one of the gumma, a criterion that no longer suffices for the pathological recognition of syphilitic lesions. On the other side, C. Steinberg[3] says that syphilis leads frequently to interstitial inflammation and induration of the pancreas.

In the six cases of diabetes presented above an interstitial pancreatitis, both interlobular and interacinar, but in all chiefly the latter form, associated with disappearance of the islands, is shown. In all six cases syphilitic lesions are shown in other organs. In one case spirochetes were found in the pancreas itself, making this case positively one of syphilitic pancreatitis associated with diabetes. I think it is reasonable to decide that all six cases have the same etiology.

Are the pancreatic changes the cause of the diabetes, and is syphilis a chief factor in the etiology of diabetes by causing the lesion (interacinar pancreatitis implicating the islands) most commonly associated with diabetes? In order to settle this question the pancreas in each of the other thirty-nine cases of old latent syphilis reported in Warthin's paper on "The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or 'Cured' Syphilis" is being studied. A preliminary survey of sections from each of these cases shows that the *pancreas is not normal in a single one of these old cases of syphilis.* In every one a more or less wide-spread interacinar and interlobular (mixed) pancreatitis is found, sometimes in widely scattered areas, in other cases more severe and wide-spread. The essential pathology is the same in all: interacinar and interlobular fibrosis; disappearance of the islands of Langerhans through hyaline fibrosis; atrophy, compensatory hypertrophy, and regenerative new formation of acini; localized lymphocyte and plasma-cell infiltration. Hypertrophic islands are found, but no newly formed ones. The severity of these changes varies greatly in different cases and in different parts of the same organ. The process is essentially a *patchy* one, except in the most severe cases, when it may involve the greater part of the gland. The tail and body of the organ are always more involved than the head.

---

[2] Osler's System.

[3] Aschoff's Pathologische Anatomie, Band ii.

In the 41 cases of latent syphilis already reported there were six cases that showed on preliminary study very marked changes in the pancreas. Two of these were the two cases of diabetes, Cases III and IV, of this paper. The other four cases had no clinical history of diabetes or glycosuria. It is possible that they might have had it without symptoms, so that it was not discovered clinically, as the patients were all over forty years of age. It does not seem probable, however, that it was missed. As far as it is possible to tell without sectioning the greater part of the organ, the pancreatic changes in these four non-diabetic syphilitics are precisely the same and apparently as marked as in the diabetic cases. On going over our autopsy slides for a number of years back and examining slides of pancreas from our syphilitic cases a number of non-diabetic cases were found presenting similar marked interacinar pancreatitis. It would seem, therefore, that if the degree of change is not the factor responsible for the diabetic symptoms there must be some other explanation of the latter. Possibly associated changes in liver, adrenals, hypophysis, etc., may be necessary to produce the diabetes phenomena. If this is true we have no knowledge of such changes at this time. In the meantime we are making a comprehensive study of the pancreatic changes associated with syphilis, and shall make a full report of these later.

CONCLUSION. Our material shows that a combined interlobular and interacinar type of pancreatitis with loss of the islands of Langerhans is extremely frequently associated with old latent syphilis (practically all of our cases). That in the great majority of cases the pancreatitis is localized and patchy in character, and more rarely severe and diffuse. That diabetes may be associated with the more marked degrees of syphilitic pancreatitis; and in our autopsy service all of our diabetes cases have been so associated; but that a number of cases of syphilitic pancreatitis of similar degree of severity have not presented the clinical symptoms of diabetes. It seems very probable, therefore, that *latent syphilis is the chief factor in the production of the form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis.*

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Edited by George Morris Piersol, M.D. Monthly. Illustrated. 1920 pages yearly. Price, $5.00 per annum.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, founded in 1820, has long been recognized as the leading medical journal of the English-speaking race. From the first it sought the epoch-making papers, and becoming recognized as their medium, it has, in turn, been sought by those who have had discoveries or real advances in the art and science of medicine to announce in its Department of Original Articles. During 1916 *The American Journal* will still further develop a feature that has proved most useful and popular, namely, a series of Special Articles, written by prearrangement with men of the highest authority, and covering present-day topics of the greatest importance and interest. These articles are designed to be clinical and practical, and to present important advances and the latest knowledge clearly and concisely, with particular reference to application in daily work. The Department of Book Reviews will continue to comprise critical and discriminating estimates of important new books, as well as briefer notices of books of less importance and of new editions. The Department of Progress of Medical Science, under the charge of recognized specialists, will continue to summarize the actual advances in the art and science of medicine appearing in the leading medical periodicals of the world.

PROGRESSIVE MEDICINE

A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES, COVERING THE ENTIRE DOMAIN OF MEDICINE. Edited by Hobart Amory Hare, M.D., Professor of Therapeutics in Jefferson Medical College, Philadelphia; Physician to the Jefferson Medical College Hospital, etc. Assisted by Leighton F. Appleman, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. **In four octavo volumes, containing 1200 pages, amply illustrated. Annual subscription price, in heavy paper covers, $6.00, *net;* in cloth binding, $9.00, *net.* Carriage paid to any address.**

PROGRESSIVE MEDICINE is the story of the progress, discoveries and improvements in the various branches of the medical and surgical sciences, and is published four times a year, in March, June, September and December. The matter presented is the digested essence of the entire medical literature of the world published during the previous twelve months, modified, explained and criticised in the light of the personal experience of the contributor. By this method useless information is discarded and only that which is valuable and really helpful to the practitioner is retained. Practicality and thoroughness are the controlling features. The contributors are authorities in their respective lines, and their experience in private and hospital practice enables them to choose unerringly that which their brother workers require. Every article is original, the veritable product of the author whose name it bears. The style is narrative in form, hence easy to read. The interpretation of the facts stated is given and their bearing upon the whole subject under consideration is clearly and simply indicated.

COMBINATION RATES

The American Journal of the Medical Sciences .	per annum, $5 00
Progressive Medicine (heavy paper covers)	" 6 00
Progressive Medicine (cloth binding)	" 9 00
Progressive Medicine (paper covers) and the American Journal	**" 10 00**

PHILADELPHIA
706-8-10 SANSOM ST.

LEA & FEBIGER

NEW YORK
2 WEST 45TH ST.

Myxoma-Like Growths in the Heart, Due to Localizations of Spirochaeta Pallida

PLATES 1 TO 4

ALDRED SCOTT WARTHIN

Reprinted from The Journal of Infectious Diseases
Vol. 19, No. 2, Aug. 1916, pp. 138-144

MYXOMA-LIKE GROWTHS IN THE HEART, DUE TO LOCALIZATIONS OF SPIROCHAETA PALLIDA

PLATES 1 TO 4

ALDRED SCOTT WARTHIN

From the Pathological Laboratory of the University of Michigan, Ann Arbor

In 5 cases of congenital syphilis of infants round translucent nodules have been found in the myocardium, appearing to the naked eye as myxoma-like growths. Three cases were new-born infants dying a few days after birth, one was a child 14 months old, and one a child 18 months old. Of these cases 4 presented signs of syphilis and showed the presence of spirochetes in other organs and tissues; while 1 showed syphilis only in the myocardium.

The myxoma-like nodules occurred in all cases in the anterior wall of the left ventricle, either near the apex or near the ventricular septum. In 1 case a similar nodule was found on the posterior wall of the left ventricle. In 3 cases there were two distinct nodules in the anterior wall of the left ventricle, one just above the apex, the other higher, over the septum. The nodules, which appeared to be nearly round or ovoidal, spherical on section, were all elevated above the general level of the epicardium. The largest were 1 cm. in diameter; the smallest was 5 mm. They extended entirely through the heart-wall from epicardium to endocardium, projecting inwardly as well as outwardly on the epicardial surface. They were light-grayish in color, of a translucent and jelly-like quality, with a few prominent, tho small, blood-vessels running over or around them. Their consistence was that of mucoid tissue. In all respects they resembled small myxomas, and the first ones seen were at first sight so regarded. The hearts of the five infants were much enlarged, dilated, and hypertrophic, the walls of the left ventricle being 2 or 3 times thicker than normal. Smaller translucent areas also occurred throughout the myocardium.

On microscopic examination these round translucent areas were found to consist of an edematous gelatinous connective tissue, showing remains of atrophic muscle fibers, especially at the periphery. Microscopically the nodules were distinctly intramural, not quite reaching the endocardium, being separated from it by a thin band of heart muscle. A similar intervening thinner band was also present on the epicardial side. In the center of some nodules the muscle had completely disappeared. The remaining muscle fibers were arrayed somewhat like the meridians of longitude on a globe, farther apart at the equator, and converging at the poles. The space between the pressed-apart fibers was filled in with the mucoid connective tissue. Mucin stains, particularly cresyl violet, gave a strong mucin reaction. The gelatinous tissue was not very cellular, except in areas, the cells being chiefly varied forms of fibroblasts (epithelioid cells), lymphocytes, and plasma cells. Many of the fibroblasts had numerous branching processes, but the branching was not so marked as that in ordinary gelatinous tissue. The intercellular substance was semifluid or mucoid, or consisted of delicate fibrillae in a semifluid matrix. The histologic changes were precisely the same in kind as those between the heart-muscle fibers in spirochetosis of the myocardium, tho differing in degree, in greater mucin content, sharper localization, and greater destruction of muscle fibers. The changes in the muscle fibers indicated a process that was spreading peripherally from a center of more marked change. This central, presumably older, area showed no signs of caseation, fatty change, or fibrosis; it appeared simply more semifluid, or mucoid, than the peripheral portions. No new formation of blood vessels was shown. The cellular infiltration and proliferation were so slight that microscopically the nodule might easily have been taken for an edematous or hydropic area, or, when mucin stains were used, for a myxomatous area in the myocardium.

In sections prepared according to Levaditi's method, these mucoid areas were found to be localized colonies of Spirochaeta pallida occurring in enormous numbers. The smaller mucoid patches throughout the myocardium likewise showed Spirochaeta pallida in great numbers. The larger round sharply localized mucoid areas might be regarded as representing a mucoid granuloma or myxogumma, altho there was no histologic resemblance to the ordinary gumma of late syphilis.

In the literature I have been unable to find any microscopic description exactly fitting these lesions. In the older literature on syphilis, there are not infrequent macroscopic descriptions of the gummata of late acquired syphilis as being semitranslucent, gelatinous, or mucoid in character, but the microscopic picture of such macroscopic gelatinous gummata as described does not in any way resemble these lesions.

Only one instance occurs in the literature of an observation of a syphilitic lesion that was most probably of the same character as those found in my cases.

Shattuck[1] exhibited before the Pathological Society of London, in 1881, a specimen of a "mucous tumor of heart (syphilitic gumma?)," with the following description:

> "The heart of an infant, in connection with the right ventricle of which there had been formed a small circumscribed, slightly nodular and granulated ovoidal tumor, about a centimeter in its chief diameter, which slightly overhangs its base and projects into the ventricle from the anterior wall immediately below the corresponding cusp of the pulmonary valve, the inferior side of which it also involves.
>
> "*Histology.*—A net-work of delicate connective-tissue in the meshes of which lie large many-branching, granular, indented cells, of which the processes form a secondary, closer reticulum. The other organs were healthy. From a child congenitally syphilitic."

Shattuck's observation was made long before the spirochete became the positive identification of a syphilitic lesion, yet his gross and histologic descriptions make it extremely likely that the lesion he described is of the same nature as the mucoid nodules in my five cases, in which Spirochaeta pallida occurred in great numbers, proving conclusively that the lesions were due to syphilis.

If myxoma-like nodules can be produced in the heart-wall by local colonization of spirochetes, the question at once arises as to the true nature of the mucoid nodules described under the heading of myxomas of the heart-wall. The myxoma is regarded as one of the common forms of the relatively very rare primary neoplasms of the heart; but the real nature of these neoplasms has occasioned much discussion among pathologists. I have found reports of 48 such cardiac myxomas in the literature. Of these, 24 were recorded found in the left auricle, 3 in the left ventricle, 2 in the right auricle, 2 in the right ventricle, 1 involving both auricles, 3 on the aortic valves, 2 on the mitral, 8 on the tricuspid, and 3 on the pulmonary valves. The majority were endocardial in origin, either firmly connected with the endocardium, or rising therefrom by a pedicle, giving the mucoid nodule the appearance of a polypoid myxoma. Only in a few cases has the apparent myxoma been imbedded in the heart-wall or shown such intimate relationship as to convey the impression that the growth was intramural, not endocardial, in origin.

These so-called myxomas of the heart have been small in size, and clinically unrecognizable, being discovered only by accident at autopsy. They have been called myxomas because of their translucency and their histologic appearance of branching cells, with fine fibrillae and semifluid intercellular substance. Staining tests for mucin have either

---

[1] Tr. Path. Soc. London, 1881, 32, p. 77.

EXPLANATION OF PLATES

PLATE 1

FIG. 1. Heart of infant dying from congenital syphilis. Two mucoid nodules (myxogummas) in anterior wall of left ventricle near septum. Left ventricle hypertrophic and dilated.

FIG. 2. Heart of infant dying from congenital syphilis. Two mucoid nodules in anterior wall of left ventricle, above apex and involving part of septum. Entire heart light-colored and more translucent than normal as a result of diffuse interstitial mucoid proliferation or edema caused by diffuse spirochetosis. Mucoid nodules contained enormous numbers of spirochetes.

PLATE 2

FIG. 3. Transverse section of mucoid nodule seen in Fig. 1. Nodule extends through myocardium, is elevated on epicardial and endocardial sides, but separated from epicardium and endocardium by narrow bands of muscle. The bluish fibrillar areas in the nodule are the mucoid areas containing spirochetes. Bands of pale atrophic muscle found throughout entire translucent area. The appearances are those of localized myxedema of the myocardium with atrophy and degeneration of muscle rather than of localized granulomatous proliferation (gumma). Hematoxylin and eosin.

PLATE 3

FIG. 4. Section of translucent area stained with cresyl violet. Pink fibrillae show marked mucin reaction between muscle fibers.

PLATE 4

FIG. 5. Section of the myxoma-like nodule in Fig. 2, from half of nodule prepared by Levaditi's method. Drawing made from photomicrograph showing actual number of spirochetes appearing in one focal field, with those partly out of focus represented as in one focal plane.

PLATE 1

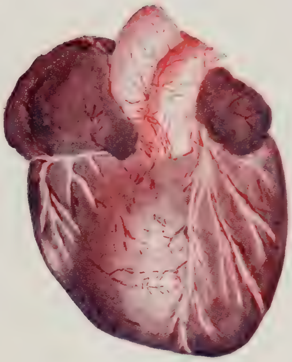

Figure 1

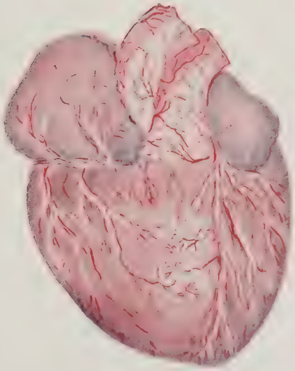

Figure 2

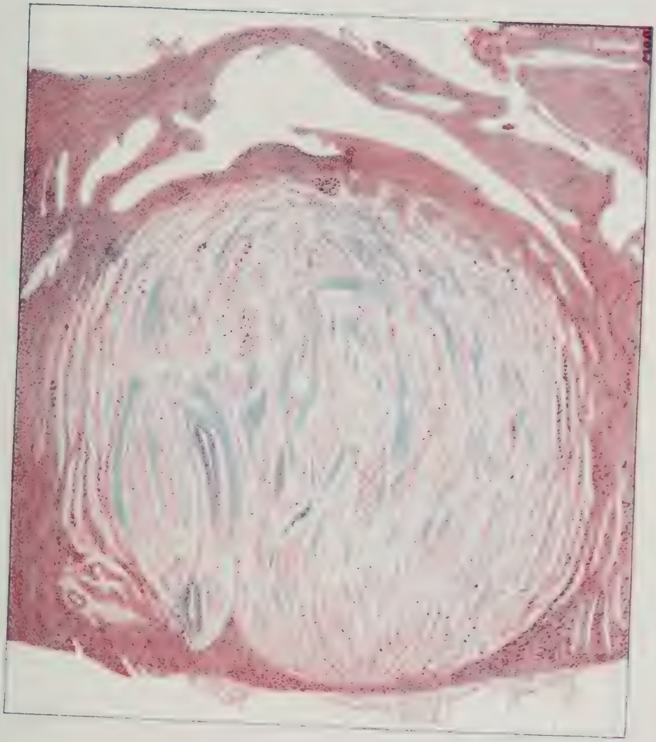

Figure 3

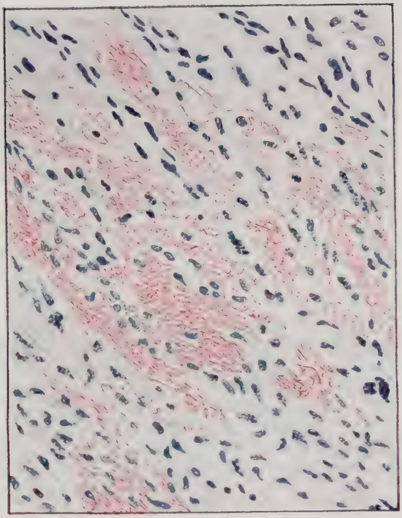

Figure 4

PLATE 4

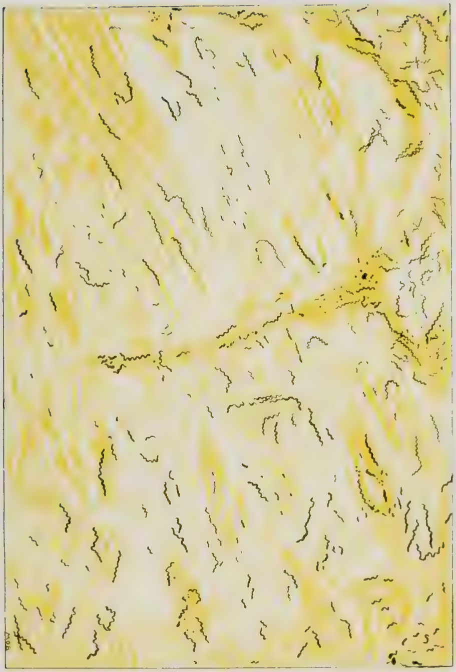

Figure 5

not been tried, or have resulted negatively, with the exception of Hanser's[2] case in which positive mucin tests with mucicarmin and thionin were obtained. These reactions Hanser used as positive argument to prove the true myxoma nature of the little polypoid translucent nodule, the size of a cherry stone, which he had found springing from the anterior papillary muscle of the mitral. The location of the growth, the mucin reaction, the absence of blood pigment, and the presence of elastic fibers he regarded as proof of the true neoplastic character of this tumor.

On the other hand, it is asserted that the majority of these endocardial mucoid nodules represent organized thrombi, or inflammatory proliferations of the endocardium, those on the valves in part belonging to the so-called "Lambl's excrescences." I myself have had 2 cases of endocardial mucoid nodules undoubtedly originating as organizing thrombi.

Case 1.—Old acquired syphilis. Angina pectoris. Sudden death. Chronic syphilitic myocarditis. The right auricular appendix was completely filled with a translucent mucoid tissue, attached to the surface of which the remains of an old thrombus could still be seen with the naked eye. Microscopically, the mucoid area presented the appearance of myxomatous tissue, giving good reactions for mucin, mostly devoid of any blood pigment or fibrin, and containing new-formed elastic fibers. Between the myxomatous connective tissue and the thrombus lay an intermediate area of beginning organization and formation of a young gelatinous fibroblastic tissue. Here there could be not the slightest doubt that the myxomatous tissue represented simply the organization of a thrombus attached to the endocardium, for all stages of the process of the organization and development of the mucoid tissue could be seen. As this observation took place before the discovery of the spirochete no examination for spirochetes was made.

Case 2.—Old acquired syphilis. Angina pectoris. Sudden death. Gummatous myocarditis of left ventricle. Thrombosis of left ventricle. Organizing thrombus attached to thinned heart wall just above apex. Next to the heart wall, which at this point was mostly fibroid, the organizing thrombus presented a layer of mucoid tissue, giving reactions for mucin, in chief part containing no blood pigment, and showing new-formed elastic fibrillae. No examination for spirochetes was made.

There can be no doubt that endocardial nodules of mucoid tissue arise from the organization of parietal thrombi, and it is most probable that all the reported cases of cardiac myxoma in which the supposed neoplasm was attached to the endocardium, were not neoplasms, but polypoid formations of a young mucoid fibroblastic tissue, arising from the organization of a thrombus.

---

[2] Frankfurter Ztschr. f. Path., 1911-12, 9, p. 362.

Fibroblastic proliferations of the endocardium, particularly of the valvular endocardium, show a particular tendency toward the formation of a mucoid connective tissue that gives a more or less pronounced staining reaction for mucin. It has been my experience that in every organizing valvular vegetation, some of the new-formed connective tissue gives in its earlier stages such mucin-staining reactions. The occurrence of mucin in organizing cardiac thrombi has been noted by other writers. Wegelin[3] states that "the mucin-reactions often give a positive result in the organization of thrombi of the heart wall." Brenner, Czapek, Curtis, Lubarsch, and others, also recognize the mucoid character of organizing thrombi.

In not a single one of the reported cases of supposed myxoma attached to the endocardium is the blastoma nature of the mucoid tissue conclusively demonstrated. On the contrary, the evidence given points to the origin from organizing thrombi. They should therefore be rejected as true cardiac neoplasms, and no longer classed with such. A true myxoblastoma of the endocardium is yet to be demonstrated. This applies also to the relatively few intramural mucoid nodules reported as myxomas. From the given descriptions I do not believe that any of them has been a true blastoma. My own five cases show conclusively that mucoid nodules, giving positive mucin tests, occur in the myocardium in cases of congenital syphilis and represent formations of a mucoid fibroblastic tissue due to the localization of large colonies of Spirochaeta pallida. The few intramyocardial myxomas reported (Czapek, Hlava) were probably of the same nature as the nodules which I have described, but Shattuck's case is the only one in which a syphilitic origin was suspected, and the only one in which we may be reasonably sure that the pathologic conditions were the same as in my cases.

I have shown elsewhere that in congenital myocardial syphilis the new-formed interstitial connective tissue is frequently mucoid or edematous in type, and gives a mucin reaction with cresyl violet. In the average case these mucoid proliferations are too small to be seen individually with the naked eye, but may be so extensive as to make the entire heart wall more translucent and lighter in color, as shown in Fig. *2*. Larger, more sharply localized colonies of spirochetes rarely produce the larger localized mucoid nodule seen in my cases. These myxogummas are probably relatively rare, or they could hardly have escaped observation to the degree that they have; yet I believe that

[3] Frankfurter Ztschr. f. Path., 1911 12, 9, p. 117

more detailed examinations of the hearts of congenitally syphilitic infants and children will show a more common occurrence than we now suppose. In my own experience, the myxogumma of congenital syphilis is more frequent than the caseating gumma of the heart in acquired syphilis, of which I have seen only one example.

SUMMARY

Localized colonization of Spirochaeta pallida in the myocardium in congenital syphilis may lead to the formation of an intramural mucoid nodule, from 5 to 10 mm. in diameter, resembling mucoid tissue both macroscopically and microscopically, and giving a positive mucin reaction. Such myxogummas are relatively rare, and may be mistaken for myxomas.

A mucoid fibroblastic tissue giving positive mucin reactions is very commonly produced in the organization of parietal cardiac thrombi and valvular vegetations. The absence of blood pigment, the positive mucin reaction, and the presence of newly formed elastic fibers cannot, however, be taken as points deciding the blastoma character of the mucoid tissue.

There is no positive proof of the occurrence of a true myxoblastoma of the heart. The mucoid nodules attached to the endocardium are undoubtedly organized thrombi; the rarer ones in the myocardium may most plausibly be interpreted as myxogummas, or proliferations of a mucoid fibroblastic tissue caused by the localization therein of Spirochaeta pallida.

The Staining of Spirochaeta Pallida in Tissues

By Aldred Scott Warthin, Ph.D., M.D.,
Ann Arbor, Michigan.

Reprinted from The International Association
of Medical Museums, Bulletin No. VI
August 1, 1916

THE STAINING OF SPIROCHAETA PALLIDA IN TISSUES.*

ALDRED SCOTT WARTHIN, Ph.D., M.D.,
Ann Arbor, Michigan.

The demonstration of the presence of *Spirochaeta pallida* in tissues has come to be the conclusive criterion of the existence of a syphilitic infection. My own researches have shown that the presence of this parasite in the tissues occasions in the great majority of cases very slight parenchymatous atrophy and degenerations, and interstitial collections of lymphocytes and plasma-cells, with fibroblastic proliferation. The degree of these lesions is usually too slight to cause them to appear above the clinical horizon; but the tendency in these clinically cured or unsuspected cases is to run a very chronic, more or less latent, course, lasting from ten to thirty years, the ultimate results of which are parenchymatous atrophy and fibrosis with a corresponding loss of function, so that years after the initial infection, the patient appears clinically as a case of myocardial weakness, aortitis, chronic pancreatitis, diabetes, chronic nephritis, etc.; or simply shows vague and apparently inexplicable headaches, impotency, anaemia, cachexia, psychoses, etc. The pathologic interpretation of such chronic cases as latent syphilitic infections due to the presence of the spirochetes, and the demonstration of these organisms in the slight lesions in the tissues of such cases is one of the most important and far-reaching advances made in pathology. The pathology of syphilis must be rewritten; the *gumma* must be relegated to the background as a pathognostic criterion of the existence of syphilis; and important changes must be made in our ideas concerning the frequency of this infection, its treatment and its curability.

Since the diagnosis of syphilis rests wholly upon the demonstration of the spirochete in these latent cases, the methods of staining this organism become of very great importance. What can be more impressive than well-stained sections showing the tissues crowded with innumerable spirochetes;—particularly when we recall to mind that only a decade ago we looked into syphilitic tissues and saw nothing. All has been changed by the development of *staining methods,* particularly one—the method of Levaditi. I do not know of any more important and far-reaching single advance made in medicine during the last decade than this single technical procedure. Yet experimental researchers often look with a self-assumed superior righteousness and a slight contempt at the worker in technical methods and pathological histology. Have the former any victories of achievement comparable to the discovery of the spirochete of syphilis?

---

* From the Pathological Laboratory of the University of Michigan.

The diagnostic importance, therefore, of the spirochete makes all staining methods designed to show it worthy of careful trial and consideration. Relatively few methods have been developed during the decade of work with this organism; and of these only one is, in my opinion, a good method considered from all points of view. In my laboratory during these ten years we have tried out all staining methods that have been applied to the demonstration of the spirochete; and I believe that a summary of our experience will be worth while. These methods are as follows:—

I. STAINING METHODS DESIGNED TO DEMONSTRATE THE SPIROCHETE IN SINGLE SECTIONS OF TISSUE.

1. *Schmorl-Giemsa Method.*

1. Fix in 10 per cent formol. Cut very thin sections on freezing microtome.

2. Place the sections in a staining dish containing a measured amount of distilled water. To each cc. of water add one drop of Giemsa's stain. Use clean glass needles to manipulate the sections. After one hour transfer sections to a fresh solution in which they are left 5-12-24 hours.

3. Wash quickly in a concentrated solution of potassium alum, then quickly in water.

4. Mount in glycerin-gelatin; dry on the slide until nearly dry; blot with xylol or cedar oil and mount in xylol or cedar oil or neutral balsam. Do not use alcohol.

The spirochetes are stained pale lilac or reddish violet and can hardly be distinguished from the deeply stained background.

Various modifications of the staining of spirochetes in sections by means of Giemsa's stain have been suggested, but in all of these the spirochetes are stained so lightly that the methods have but little practical value. Rarely is it possible to photograph spirochetes in sections stained with this stain. In many cases the organisms do not stain at all; so that the failure to obtain spirochetes by this method does not in any way mean that the organisms are not present in the tissues.

2. *Nikiforoff's Method.*

1. Fix for 24 hours in equal parts of a five per cent water solution of potassium bichromate and a saturated solution of mercuric chloride in 0.6 per cent sodium chloride.

2. After-harden in graded alcohols in the incubator.

3. Imbed in paraffin.

4. Stain 24 hours in a mixture of alcoholic one per cent solution of tropaeolin, 5 cc., concentrated watery methylene-blue solution, 10 cc., and caustic potash (1:1000), two drops.

5. Wash in water.

6. Dip several times in a mixture of equal parts of absolute alcohol and ether.

7. Oil of bergamot; xylol; balsam.

This method is also unsatisfactory and of no practical use. The spirochetes are often not stained, and when stained are barely visible.

In general I would say that no satisfactory staining of spirochaeta pallida in tissue-sections can be obtained by any of the aniline dyes.

II. Silver-Impregnation of Sections of Tissues.

Ferguson-Bielschowsky Method.

1. All methods of fixation applicable.

2. Imbed in paraffin. Fix sections on slide with albumin fixative.

3. 12-24 hours in a two per cent solution of silver nitrate.

4. Transfer for 15-30 minutes to a freshly prepared alkaline silver solution (20 cc. of a two per cent silver nitrate solution to which are added three drops of a 40 per cent caustic soda solution, and the precipitate redissolved by adding ammonia drop by drop while stirring).

5. Rinse quickly in distilled water; then place in 20 per cent formalin for three minutes or until the sections are black.

6. Wash in distilled water, and place for ten minutes in an acid gold bath (10 cc. distilled water to which are added 2-3 drops of one per cent gold chloride and 2-3 drops of glacial acetic acid).

7. Immerse in five per cent hyposulphite ½-1 minute to remove all unreduced silver.

8. Wash in distilled water; dehydrate; clear in xylol; mount in balsam.

This method stains both reticular fibers and spirochetes deep grayish brownish black, according to the degree of toning which can be varied to taste. With this method there is, therefore, no differentiation from reticulum as far as staining effects are concerned; and the recognition of the spirochete must rest upon pure-

Its morphological features. For an expert worker with the organism this is a safe procedure; but for the novice it would not be safe without control. The method has, however, the great advantage of being applicable to any fixation, economical in time, and applicable to single sections.

III. The Levaditi Method and Its Modifications.

1. *Levaditi's Method.*

The original method of Levaditi gives the most successful staining of the spirochetes of syphilis in tissues. If the method is followed in the most painstaking manner, and if the following conditions are observed it will in the hands of an experienced worker give most beautiful and constant results.

1. The tissues must be fresh, and fixed immediately after removal from the body. Spirochetes rapidly disappear from the body after death. Evaporation, cold, excessive moisture, beginning putrefaction, etc., all affect the staining power of this organism. In tissues removed from the body and allowed to stand 6-8 hours or more without fixation the spirochetes are found clumped, beaded, fragmented, devoid of coils, slightly wavy, etc.

2. The formol used must be neutral, free of tannin, formic acid or vegetable coloring matter. The formol solution should be made preferably in a physiologic salt, or Ringer's solution. The formol may be neutralized by adding powdered marble or calcium carbonate to the stock bottles.

1. Fix thin pieces of tissue (3-4 mm.) in 10 per cent neutral formol solution for 24 hours. Formol-Müller's and alcohol fixation may also be used but the results with these fixations are more uncertain.

2. 24 hours in 90 per cent alcohol.

3. In distilled water until tissue sinks.

4. Impregnation in incubator in a 1.5-3 per cent silver nitrate solution for 3-6 days.

5. Wash in the dark in distilled water for 15-30 minutes.

6. Reduce for 48 hours, in the dark, at room-temperature, in a solution of pyrogallic acid 4 gms., 40 per cent formol 5 cc. and distilled water 100 cc.

7. Wash in distilled water thoroughly. Imbed in paraffin. Cut very thin sections. Toluidin-blue or Giemsa may be used as a contrast stain.

The spirochetes are dark brown to black against a yellow background. If properly managed the reticulum will be yellowish and not resemble the spirochete in staining quality. If carelessly managed silver precipitates will be found around the borders of the block, or even entirely through it, and the reticulum or even the entire section may be uniformly black. Experience is needed to gain perfect control of the method. In a well-prepared section the black spirochetes contrast well against the yellow background, and no contrast stain is necessary. In sections of brain or spinal cord a yellow background is obtained with greater difficulty because of the impregnation of fine neuroglia and nerve fibers by the silver. Careful manipulation of the method can, in expert hands, give sections in which the fibers and spirochetes are well differentiated. The longer the tissue is fixed in formol, the greater the impregnation of the spirochetes and the less that of the fibers. If fairly thick pieces of tissue (5 mm. and over) are used the spirochetes in the central portion of such pieces will be found to be more deeply impregnated than the neuroglia fibers.

2. *Levaditi's Pyridin Method.*

1. Fix thin pieces of tissue 24 hours or longer in 10 per cent formol.
2. 24 hours in 95 per cent alcohol.
3. Distilled water until tissue sinks.
4. Impregnation at room-temperature for 2-3 hours, and in incubator at 50-55°C. for 3-5 hours in the following solution:

1 per cent silver nitrate solution	90 cc.
Purest pyridin	10 cc.

5. Without washing, transfer directly to the following:

4 per cent pyrogallic acid solution	90 cc.	85 cc.
Pure acetone	10 cc.	
Purest pyridin		15 cc.

Reduce in this solution 6-9 hours.

6. Wash for 2 hours in several changes of distilled water, or until the odor of pyridin is entirely lost.
7. Dehydrate in water-free acetone or alcohol, clear in xylol, imbed in paraffin, and cut sections 2-3 microns thick.

It is essential that all solutions should be absolutely clean and filtered into the bottle containing the tissues. Our experience with this method has been much less satisfactory than with the original method, so that we no longer use it.

3. *Noguchi's Modification for Nerve-Tissues.*

1. Fix brain in 10 per cent formol.

Take pieces 5-7 mm. thick.

2. Leave these pieces 5 days at room-temperature in the following:

Formol	10 cc.
Pyridin	10 cc.
Acetone	25 cc.
Alcohol absolute	25 cc.
Distilled water	30 cc.

3. Wash in frequently changed distilled water 24 hours.
4. After-harden for 3 days in 96 per cent alcohol.
5. Wash in frequently changed distilled water for 24 hours.
6. Impregnate in a 1.5 per cent silver nitrate solution in a dark flask for 5 days at room-temperature or for 3 days at 37°.
7. Wash 2 hours in distilled water.
8. Reduction in a 4 per cent pyrogallic acid solution in a 5 per cent formol, for 24-48 hours at room temperature.
9. Wash thoroughly in distilled water.
10. 80 per cent alcohol for 24 hours.
11. 96 per cent alcohol for 3 days, changing several times.
12. Absolute alcohol for 2 days.
13. Imbed in paraffin.

Sections should be taken from different depths of the block in order to find the zone in which there is the best differential impregnation of the spirochetes and fibers. In such areas the spirochetes should be black against a yellowish or yellowish brown background. In our experience, however, no better results have been obtained by this method than by the original Levaditi, provided that the tissues have been properly fixed in formol and after-fixed in alcohol.

d. Nakano's Modification of Levaditi's Method.

1. Fix thin pieces in 10 per cent formol 10-20 minutes at 37°.
2. After-harden 3-5 hours in 95 per cent alcohol.
3. Wash in running water 10 minutes, then 10 minutes in distilled water.
4. Impregnate in a 1.5 per cent silver nitrate solution in dark flask, for 4-5 hours at 50°.
5. Reduce in a 4 per cent pyrogallic acid in 5 per cent formol solution for 4-10 hours at 50°.
6. Wash in water.
7. Imbed in paraffin.

This abbreviated Levaditi is not to be recommended, as the results are very uncertain.

5. *Yamaota's Modification.*

1. Fixed as desired. Take thin pieces (5 mm.), wash 24 hours in running water, and 1 hour in distilled water.

2. Impregnation in 5 per cent silver nitrate solution 48 hours at 37°.

3. Reduce 24 hours at 37° in the following mixture:

Tannic acid	1
Pyrogallic	2
Distilled water	100

Change fluid if it becomes cloudy.

4. Wash 1 hour in water.

5. Imbed in celloidin. Counterstain with Löffler's methylene blue. Clear in origanum oil. Balsam.

Only the spirochetes are impregnated; and very good results can be obtained by this method. The failure at any time to obtain spirochetes cannot be taken as a positive evidence that they are not present.

6. *Eyene's and Sternberg's Modification.*

1. Thorough fixation in 10 per cent formol. Cut on freezing microtome, or imbed in celloidin.

2. Wash sections in distilled water, and place them in a 1 per cent silver nitrate solution 30-35 minutes in the incubator in the dark, or longer at room temperature in the dark.

3. Place sections in the following until they become dark (1-2 minutes). Remove before a precipitate occurs:

2.5 per cent silver nitrate	10 cc.
10 per cent aqueous gelatin (warm)	10 cc.
50 per cent aqueous gum Arabic	10 cc.
5 per cent aqueous hydroquinone	5 cc.

Mix well, adding the hydroquinone after the others have been thoroughly mixed.

4. Wash 1-2 minutes in a 10 per cent aqueous solution of sodium hyposulphite.

5. Wash in water, dehydrate, clear and mount.

Because of the excessive precipitates usually produced, this method is of little value to the ordinary diagnostician. As with most of the silver-impregnation methods improvement in results follows familiarity with the method.

Conclusion.—For the demonstration of the *Spirochaeta pallida* in tissues the silver-impregnation method of formol-fixed tissue according to the method of Levaditi offers the best results, and in expert hands becomes an almost perfect method. It can be readily seen that the essential features of the method,—fixation, impregnation and reduction,—offer a wide range of variation and modification, and that the individual worker will modify these factors until he secures the results that to him seem most reliable and satisfactory. In the writer's experience the following modification seems to be the best of all:

7. *Warthin's Modification of the Levaditi Method.*

1. Tissues must be as fresh as possible. Fix while warm, if possible. Blocks should not be more than 5 mm. thick.

2. Fix 3-10 days in the following:

Sodium chloride	0.9
Sodium bicarb.	0.01
Potassium chloride	0.02
Calcium chloride	0.02
Formol	10 cc.
Distilled water	100 cc.

The formol must be colorless and free from tannic acid. A perfectly neutral 10 per cent formol solution may also be used for fixation. The longer the formol fixation, the better the silver-impregnation will be.

3. Wash in frequently changed distilled water 24 hours.

4. After-fixation in 95 per cent alcohol for 3 days.

5. Wash in frequently changed distilled water 24 hours.

6. Impregnation in 2 per cent silver nitrate solution, in the dark, in the incubator for 3 days.

7. Wash thoroughly in distilled water, in the dark.

8. Reduce for 48 hours, in the dark, at room temperature, in the following:

Pyrogallic acid	4 gm.
Formol	5 cc.
Distilled water	100 cc.

9. Wash thoroughly in distilled water.

10. 80 per cent alcohol 24 hours followed by 95 per cent, and absolute.

11. Imbed in paraffin as usual. Cut thin sections. Counterstains not useful.

Spirochetes are dark brown to black against a pale yellowish background. If the method is carefully followed there will be no precipitates. Especial attention should be paid to thorough washing and to impregnation and reduction in the dark.

THE ANN ARBOR PRESS

Some Substitutes for Glass for Covering Microscopical Sections

I. Gelatin II. Pyralin

By Carl Vernon Weller, M.S., M.D., Assistant Professor in Pathology, University of Michigan.

(From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.)

Reprinted from The International Association
of Medical Museums, Bulletin No. VI
August 1, 1916

SOME SUBSTITUTES FOR GLASS FOR COVERING MICROSCOPICAL SECTIONS.*

I. GELATIN. II. PYRALIN.

CARL VERNON WELLER, M.S., M.D., ASSISTANT PROFESSOR IN PATHOLOGY, UNIVERSITY OF MICHIGAN.

(From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.)

The difficulty in obtaining suitable cover-glasses, especially those of the larger sizes, during the past year, has emphasized the need for continued search for a substitute material. This, to be available, must be a substance which can be applied so as to form a thin protective covering over the section. It must be, also, practically colorless, transparent, permanent and of such optical properties as will permit the use of objectives intended primarily for viewing sections covered with glass. In regard to this last consideration it must be borne in mind that any material which will permit the use of low power objectives will still be very useful even if its optical properties are such that it is not well adapted to work beneath an oil immersion objective or in microphotography.

Although no substitute has been found which can in all respects take the place of glass for covering microscopical sections the two materials and methods presented here have proven adeuate for certain kinds of work.

I. Gelatin. Very serviceable and permanent mounts of microscopical sections can be made by Nieuwenhuyse's modification of Liesogang's method of mounting in gelatin. This method, as applied to single unfixed sections, has been described in Bulletin No. V of this Association. We have found it equally applicable to paraffin sections handled by dextrin or molasses fixative celloidin sheet method or when fixed to the slide by the albumin method. Its range of usefulness can therefore be extended to include the mounting of series of sections.

---

* Read at the Meeting of the American Section, International Association of Medical Museums, Washington, May 8th, 1916.

The method is as follows: The sections after staining are transferred from water to a thick gelatin prepared by soaking 1 part best gelatin in 3 parts of cold water, raising the temperature to 50 degrees C and filtering. This gelatin solution is solid at ordinary temperatures but is liquid at 37 degrees C at which temperature it is used. The sections either in the celloidin sheet or fixed to microscopical slides are left in the warm gelatin in the incubator or drying oven for about twenty minutes. If the celloidin sheet method is being used, the celloidin should be cut into sections of the size desired for mounting before being placed in the gelatin. The glass slides, thoroughly cleaned, are then warmed by flaming and a few drops of the liquid gelatin placed upon each. The sections are then placed upon the slides letting them down upon the glass from one end in such a manner as to exclude air bubbles. A few drops of liquid gelatin are then placed upon top of the section and leveled off with a warm glass rod. The amount to be used depends upon the area to be covered. With a gelatin of the strength indicated above, about 1 cc. is required for every 5 cm.^{2} Upon cooling, the gelatin becomes solid and is then put in 10% formalin for 30 minutes. The preparations are then dried at a temperature (about 30 degrees) below the melting point of the gelatin until the opaque moist layer is changed into a hard transparent film.

If the sections have been fixed to slides by the albumin fixative method, the entire preparation is immersed in the melted gelatin for the preliminary infiltration. The excess of gelatin is then drained off and the under surface and margins of the slide wiped clean with gauze dipped in warm water. A few drops of gelatin may then be placed directly over the section, if needed, and leveled with a glass rod, after which the method of procedure is the same as that for the celloidin sheet sections.

As Dr. Kappers has pointed out, this method not only does away with glass covers but also makes the use of alcohol, carbolxylol, xylol and balsam unnecessary. The absolute freedom from stickiness even in the warmest weather is also a decided advantage. The chief disadvantage lies in the fact that stains readily soluble in water are either removed entirely or are diffused by the stay in the aqueous gelatin. With methylene blue, for instance, this method cannot be used. Very satisfactory results can be obtained with haemalum and eosin if the sections are properly washed in water before placing in gelatin so that the less firmly fixed portion of the eosin is removed. Another disadvantage is found in the length of time after staining before the preparation is ready for examination, several hours being required for the drying out of the gelatin to the transparent condition. For permanent preparations, where large sections, or series or groups of sections treated as one in a celloidin sheet, are to be mounted, this application of Liesogang's gelatin method furnishes a very acceptable substitute for cover-glass and can be strongly recommended for that type of work.

II. Pyralin. In searching for a celluloid product possessing properties which would permit its use as a substitute for cover glasses, our attention was called to the Pyralin Sheeting manufactured by the Arlington Company, 725 Broadway, New York. This material may be obtained in sheets 20 x 50 inches in size and in thicknesses ranging from 5/1000 to 30/1000 of an inch. It is practically transparent and colorless, save for a slight smokiness scarcely to be detected in the thinner sheets. For use as a substitute for glass the material should be polished on both sides so that it is necessary to specify size of sheet, thickness, color and finish in order to secure the proper sort. With ordinary scissors, the sheets may be cut into rectangular pieces of the size desired. These rectangular pieces of pyralin may be employed in exactly the same manner as glass for covering sections, using balsam as the mounting medium. With lower powers of the microscope it is impossible to detect any difference as compared with glass and even the oil immersion can be used quite successfully. Xylol and balsam have no effect upon pyralin and the slips may be wiped off with xylol and used repeatedly. There is, of course, no loss from breakage in handling and cleaning, and the cost of covers cut from pyralin is but a fraction of that for glass.

There is, however, one important disadvantage. Mounts which are altogether satisfactory when first made show after a day or so a tendency for the pyralin cover to curl up somewhat at the edges with a resulting retraction of the balsam. This may be prevented to some extent by using a thick balsam, warming the slide before hand if necessary.

Aside from this one difficulty, pyralin sheeting makes a very satisfactory cover material for sections and can be fully recommended if permanent preparations are not desired.

THE ANN ARBOR PRE

Note on a Case of Complete Defect of Left Half of Diaphragm, Ectopia of Liver in Left Thoracic Cavity (Hernia Diaphragmatica Spuria) with Pressure Atrophy of Left Lung

By Aldred Scott Warthin, Ph.D., M.D.,
(Pathological Laboratory, University of Michigan, Ann Arbor, Michigan.)

Reprinted from The International Association
of Medical Museums, Bulletin No. VI
August 1, 1916

NOTE ON A CASE OF COMPLETE DEFECT OF LEFT HALF OF DIAPHRAGM, ECTOPIA OF LIVER IN LEFT THORACIC CAVITY (HERNIA DIAPHRAGMATICA SPURIA) WITH PRESSURE ATROPHY OF LEFT LUNG.*

ALDRED SCOTT WARTHIN, PH.D., M.D.
(Pathological Laboratory, University of Michigan, Ann Arbor, Michigan.)

Congenital diaphragmatic hernias depend upon defective development of the diaphragm. Two forms exist: *Hernia diaphragmatica vera* in which a peritoneal sac enclosing some part of the abdominal organs projects through the defect into the thoracic cavity; and *Hernia diaphragmatic spuria* in which the ectopia of the abdominal organs takes place without any peritoneal covering. The latter form is the more common, and occurs usually on the left side in the membranous portion. The defects vary greatly in size, but are often large, and more rarely involve the entire half of the diaphragm. They arise at the time of the separation of thorax and abdominal cavity. Just what causes the disturbance of development in the closure of the communicating opening between thoracic and peritoneal cavities is not yet known; but it is certain that the development of the liver anlage is of the greatest importance in this closure, and also in determining the form and position of the diaphragm. Broman (Verhand. d. anatom. Ges. 1902, Bd. XVI, S. 9) has, in particular, emphasized the importance of the development of the liver to that of the diaphragm.

The following case of total absence of the left half of the diaphragm, with the left half of the thorax completely filled with portions of the abdominal organs, chiefly the very large left lobe of the liver, occurred in our autopsy service, in January, 1915:—

Baby K.—Born at full term, January 25, 1915. Apparently normal infant, but respirations could not be established, and after breathing a few times the infant died. Mother's personal and family history negative. No history of syphilis or of malformations in the family. Three healthy living children. Pregnancy and confinement normal.

---

* Read at the Meeting of the American Section of the International Association of Medical Museums, May 8, 1916, Washington, D. C.

Protocol.—Female baby, well developed, 51 cm. long, general nutrition good. Skin covered with vernix caseosa. Tape about umbilical cord, which is normal. No anomalies of exterior of body. Abundant hair on head, and very abundant lanugo over upper half of body. Moderate hypostasis. Greenish brown meconium coming from anus.

Abundant pale yellow panniculus. Umbilical vessels patent. Muscles very pale. About 100 cc. of clear yellow fluid in peritoneal cavity. The left half of the diaphragm is completely absent; the left lobe of the liver, the splenic flexure of the colon and a portion of the small intestine and stomach lie in the left half of the thorax. The entire liver is so rotated towards the left that it lies almost perpendicularly, its lower border turned to the left side of the body and with the large left lobe filling in the greater portion of the left thoracic cavity, extending to the height of the apex, and moulded to the form of the upper portion of the cavity. The left lobe is much larger than normal, nearly as large as the right one. The position of the liver is such that the groove occupied by the round ligament lies to the left of the ensiform and about in the middle between the two lobes. The lower border of the right lobe extends 4 cm. below the tip of the ensiform and 5 cm. below the ribs in the right nipple line. The diaphragm thins out and disappears in the coronary ligament of the liver. The coronary ligament is unusually long and membranous, and the liver is unusually movable. The spleen is free, and lies anteriorly and below the splenic flexure of the colon which extends into the pleural cavity. It is somewhat larger than normal, otherwise presents no notable features. The intestines show incomplete rotation, the appendix lying just behind the umbilicus with its long coil directed outwards, (about normal fifth month position); the caecum and ascending colon with the hepatic flexure of the transverse colon are crowded into several sharp folds lying in the epigastric region under the edge of the liver in front of the stomach, which lies vertically, extending upwards into the thorax. The left kidney lies at the brim of the pelvis; the right one is just above the brim of the pelvis. Ureters are normal. Adrenals small. Vessels normal.

The heart lies entirely to the right of the median line; and is much smaller than normal; its apex, formed by the left ventricle, points to the right. The vessels are normal. The thymus is short and 1 cm. thick in its thickest portion. It is pushed upwards

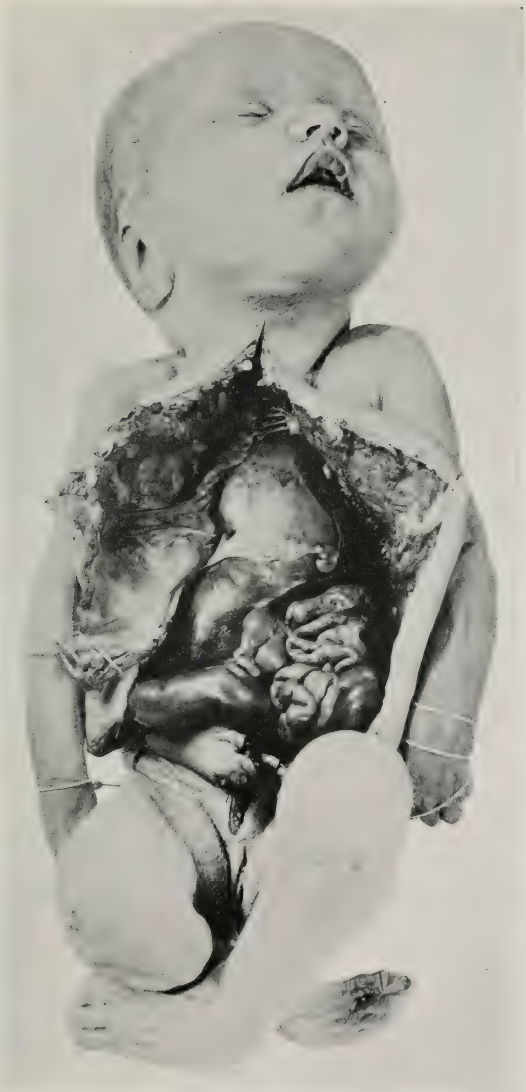

Plate I. Total absence of left half of diaphragm; liver in vertical position, the left lobe nearly filling the left thoracic cavity; incomplete rotation of intestines. Full-term foetus.

towards the right of the median line. The pericardial sac is attached to the diaphragm to the right of the median line, and to the right of the coronary ligament. The left lung is represented by two thin rudimentary lobes pressed against the heart and mediastinum. The greatest length of the left lung is 3 cm., the greatest width 2.3 cm., and the greatest thickness about 6 mm. The lower lobe is transparent, and no thicker than tissue paper. The right lung is very small (7 cm. long, 3 cm. wide) and shows three well-defined lobes.

A more minute examination of the borders of the diaphragmatic defect shows a narrow border of diaphragm 2-4 mm. broad, extending to the left of the coronary ligament. This edge is smooth, rounded, 4-5 mm. thick, and firm as if fibrous. The liver pressed directly upon this edge, and at the point of contact shows some thickening of its capsule. There are no evidences of diaphragm on the left side in the area of usual attachment.

In conclusion, this case presents total defect of the left half of the diaphragm, with a failure of rotation of the liver and part of the abdominal organs downward, so that they appear as if rotated upwards to the left into the thoracic cavity, the greater part of which is occupied by the abnormally large left lobe which pressed upon the left lung, and pushes the heart to the right. An abnormal development of the left lobe with imperfect descent and separation of the liver from the septum transversum and failure of development or pressure atrophy of the left half of the latter might be regarded as the factors leading to this defect.

COARCTATION OF THE AORTA WITH PATENT DUCTUS ARTERIOSUS.† *

CARL VERNON WELLER, M.S., M.D.,
Assistant Professor of Pathology, University of Michigan.

The heart which forms the subject of this report has proven of unusual interest for it is a very good example of that small group of cases of coarctation of the aorta in which the descending aorta appears to be a direct continuation of the pulmonary artery through a large ductus arteriosus, thus simulating, as far as the right side of the heart is concerned, a transposition of the great vessels. Associated with this anomaly and dependent upon it there has been in this case a rather unusual degree of hypertrophy of the right ventricle and a marked chronic passive congestion of the liver such that a typical nutmeg liver is presented in a child dying at the age of twelve days. A moderate degree of thymic hyperplasia was also present.

The mother of Baby C. is married and twenty-three years of age. Her family history is practically negative, as has been her own. It should be noted, however, that she is one of twins and that her twin sister is not in good health. This, her first pregnancy, was normal. She had entered the Obstetric Ward of the University Hospital, service of Dr. Peterson, but finally decided to be confined at home where she underwent a normal delivery and puerperium.

Baby C., a well developed male child, was born January 2, 1916. He remained apparently well until the ninth day when it was noted that he was not well and he was removed to the Paediatric Ward of the University Hospital, in the service of Dr. Cowie. A marked cyanosis and a loud systolic murmur rapidly developed and death occurred on the twelfth day.

At autopsy, the face showed cyanosis and icterus and the conjunctivae were congested. On opening the thorax the thymus was found to measure 6.5 cm. in length, 4.5 cm. in width, and 1.3 cm. in greatest thickness, and both right and left lobes presented definite cervical prolongations. The heart, about twice normal size, lay almost transversely, pushing the diaphragm down and presenting its apex behind the lower border of the fifth rib just outside the left nipple line. The apex of the heart was formed by the greatly hypertrophied right ventricle and a probe introduced into the thoracic aorta passed directly into this chamber, so that at first glance the heart gave the appearance of a true dextrocardia. There were numerous sub-epicardial and subpleural haemorrhages and a wedge shaped haemorrhagic area in the upper border of the upper lobe of the left lung. Aside from this area, the lungs were air-containing throughout, but showed a marked congestion and oedema.

---

† Read at the Meeting of the American Section, International Association of Medical Museums, Washington, May 8th, 1916.

* From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.

The spleen, firm and slightly larger than normal, showed a marked passive congestion. The liver was also markedly congested and mottled purplish and brownish yellow.

Microscopical sections of all organs showed a marked passive congestion but those of the liver were of special interest. The changes here were those of a marked nutmeg liver. The central zones of the liver lobules showed marked necrosis and atrophy and in some there was fibroblastic proliferation. There can be no doubt that the chronic passive congestion productive of these marked tissue changes had been operative previous to the birth of the child.

The heart from this case measures 4.8 cm. in width, 4.2 cm. in length and 3.5 cm. in thickness. The right ventricle forms about three-fourths of the total bulk and itself measures 3.4 cm. in breadth. The right ventricular wall is 7 to 8 mm. in thickness while the left measures but 4 to 5 mm.

As it emerges from the heart the aorta measures 7 mm. in diameter. This trunk gives off an innominate artery 6 mm. in diameter which appears to be a direct continuation of the aorta, while bending sharply to the left a smaller vessel, less than 5 mm. in diameter represents the aortic arch. From this the left common carotid and left subclavian are given off in normal order but are both somewhat smaller than the corresponding vessels on the right. Beyond the point of origin of the left subclavian there is a portion of the aortic arch 5 mm. in length and about 4 mm. in diameter. This enters the arterial trunk made up of the pulmonary artery, the ductus arteriosus and the descending aorta sharply at right angles.

The pulmonary artery is 1 cm. in diameter as it leaves the

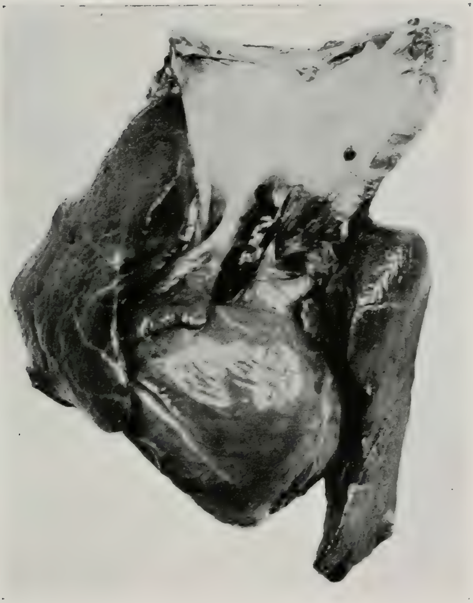

PLATE I. Extreme hypertrophy and dilatation in heart showing coarctation of the arch of the aorta and apparent direct continuation of the pulmonary artery with the descending aorta through a patent ductus arteriosus.

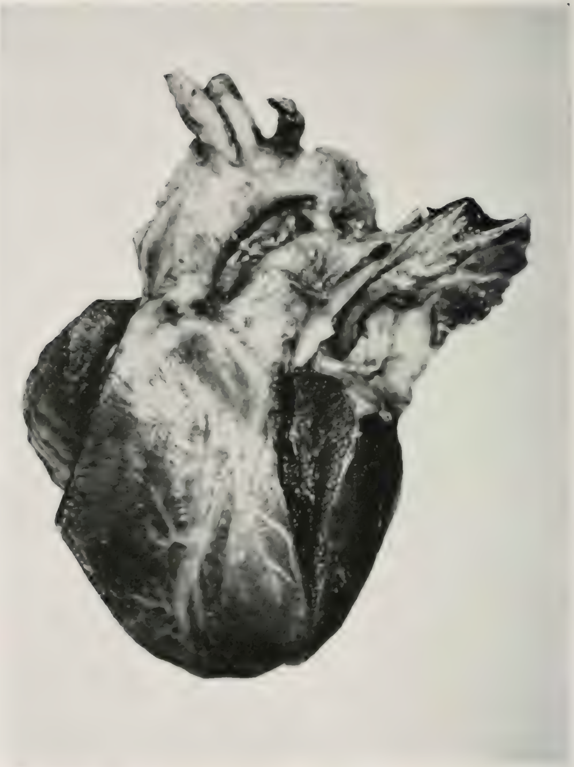

Plate II. Heart showing complete uncorrected transposition of the arterial trunks. The aorta is seen arising from the right ventricle, the pulmonary artery from the left, and occupying the usual position is the large, thick-walled ductus arteriosus.

heart. The ductus arteriosus measures 6 mm. in diameter and this lumen is but slightly increased after the portion of the vessel corresponding to the true aorta is reached.

This specimen illustrates remarkably well the apparent direct continuation of the pulmonary artery with the descending aorta through the ductus arteriosus in a certain proportion of the cases which show some coarctation of the aorta in the region of the isthmus.

COMPLETE UNCORRECTED TRANSPOSITION OF GREAT VESSELS WITHOUT DEFECT IN THE VENTRICULAR SEPTUM.*

Carl Vernon Weller, M.S., M.D.,
Assistant Professor of Pathology, University of Michigan.

Transposition of the great arterial trunks continues to be one of the most interesting of the congenital cardiac lesions. The great variety in respect to both type and degree which the condition may present, the interesting developmental problems involved and the disproportion so often noted between the marked circulatory disturbance and the relative absence (in many cases) of physical signs have served to maintain and stimulate this interest.

The heart which is here described as falling in this group is that of a male child, Baby X., five weeks' old. The family history disclosed certain hereditary stigmata. The child was born at term, well nourished, and without external anomalies. In the course of a few weeks a very marked cyanosis developed and a loud systolic murmur was heard. The child's condition grew rapidly worse, the clinical picture was dominated by the cyanosis and in the last few days life was sustained only by artificial respiration and the administration of oxygen.

At autopsy the child still showed the marked cyanosis. The head had a somewhat hydrocephalic appearance. The fontanelles were large and all the sutures gaping, with cranial asymmetry of the frontal region. The increase in intra-cranial pressure was shown also by the marked flattening of the convolutions. The ventricles, however, were small and the explanation of the increased pressure was found in the marked cerebral and cerebellar congestion and oedema.

The thymus was of normal size. The liver, purplish brown in color, extended three centimeters below the rib margin. The spleen was slightly enlarged and dark purple in color. The bladder was greatly distended, the urachus obliterated and the umbilical vessels showed nearly complete obliteration. Hydrocele in left side of scrotum.

---

*From the Pathological Laboratory of the University of Michigan.

The lungs and heart were removed together as a gross specimen. The visceral pleura was dotted everywhere with small subserous haemorrhages, averaging 3 mm. in diameter. Fewer petechiae were found in the tissues about the thymus and in the adventitia of the great vessels.

The heart measures 5.5 cm. in length and somewhat more than that in breadth because of the enormous distension of the right auricle which was filled with cruor. The cardiac apex is formed jointly by the ventricles which are of approximately the same size and thickness of wall, the left ventricular wall measuring 6 mm. and the right 5 mm. Given off from the ventricles are two large arterial trunks having at their origin approximately the normal relationships of aorta and pulmonary artery. That is to say, the vessel from the right ventricle arises in front and somewhat to the left of the one from the left ventricle. However the right ventricular trunk ascends anteriorly and passes directly into the aortic arch where the branches are given off in the normal order. The left ventricular trunk passes directly backward to give off the pulmonary branches. These trunks are both of good size and of the two the systemic aorta has the thicker and firmer wall, although this difference is not marked. In both cases the arterial orifice is guarded by three cusps which do not show the anomalous development often found in these cases. As is true in all cases of complete transposition the non-coronary cusp at the aortic orifice is the anterior one. This serves as a convenient means of estimating the extent to which rotation of the aortic septum has failed to take place, this position of the non-coronary cusp diametrically opposite the normal indicating a fault of 180° in rotation.

The ventricles are not reversed. The right ventricle receives caval blood and the left ventricle pulmonary blood. The condition is therefore incompatible with post-foetal life unless there is a persistence of either the foramen ovale or the ductus Botalli on the one hand or anomalous communications between the right and left hearts such as perforate ventricular septum on the other. In this case the foramen ovale is patent only to the extent of admitting a slate pencil, the opening being no larger than often found in the normal infant at five weeks and is, moreover, well covered by the valvula foraminis ovalis. It seems unlikely that there was much interchange of blood through this opening during the last few weeks of life.

The ductus Botalli is still patent but the opening is so small that it admits only a fine probe. From without the ductus appears nearly twice normal size and its wall is greatly thickened. It is evident that the normally occurring obliterative changes have been actively operative here.

The clinical picture presented by this case can be fully explained in the light of the progressive obliteration of the ductus arteriosus. The early period during which the child was in relatively good health was possible because of a free passage of blood through the widely open ductus. With the progressive obliteration the aeration of the blood of the systemic circulation became less and less perfect and the cyanosis progressively more intense. The systolic murmur, likewise, can best be explained as having its origin in the ductus arteriosus.

From the standpoint of congenital cardiac disease, the lesion presented by this case must be classified as a complete (180 degree) uncorrected transposition of the great arterial trunks, without perforation of the ventricular septum, without unusual patency of the foramen ovale and with the fatal outcome precipitated as a result of the physiological obliteration of the ductus arteriosus.

THE ANN ARBOR PRESS

Tubercle Bacilli in the Heart Clots in Acute Miliary Tuberculosis Complicating Chronic Lymphatic-Myelogenous Leukemia

ROBERT R. DIETERLE

Reprinted from The Journal of Infectious Diseases
Vol. 19, No. 2, Aug. 1916, pp. 263-266

TUBERCLE BACILLI IN THE HEART CLOTS IN ACUTE MILIARY TUBERCULOSIS COMPLICATING CHRONIC LYMPHATIC-MYELOGENOUS LEUKEMIA

Robert R. Dieterle

From the Pathological Laboratory of the University of Michigan, Ann Arbor

It has been shown by Wilson[1] that tubercle bacilli can be demonstrated in stained sections of blood and clots obtained at autopsy from the heart and great vessels of a case of acute miliary tuberculosis, but that, as already borne out by the clinical attempts to demonstrate tubercle bacilli in the blood by means of stained smears, culture, and animal inoculation, the number of bacilli in the circulating blood at any given moment is too small to be of any practical diagnostic value. The wide-spread dissemination of the lesions in the case studied, occurring as they did even in the bone marrow, and the very early stage (thromboses and focal necroses) of many of the lesions would seem to make it a case in which the maximal number of bacilli might be found in the blood stream. That so few (4 bacilli in one-tenth of the heart clots) were found in the heart blood at any given moment cannot be taken as an absolute index of the number of tubercle bacilli entering the blood stream from a primary focus. Rather may it show, what we already know experimentally, that tubercle bacilli entering the blood stream quickly disappear from the circulating blood. The clots and blood in the great veins and right heart should contain few bacilli, as they have dropped out of the blood during its arterial and capillary circulation. It is possible that in an ordinary case all the tubercle bacilli entering the pulmonary veins from a primary bronchial-gland focus, and passing into the arterial blood, might disappear from the venous blood by the time it reached the right heart. That this did not take place in the case described is demonstrated by the presence of bacilli in the right auricular clot, and the numerous tuberculous thrombi and hematogenous tubercles in the pulmonary vessels. Her estimate of the number of bacilli contained in the circulating blood is based solely on the number left in the venous blood after its return to the heart. The small number of bacilli found there is more an index of the number dropping out of the blood stream than of the number entering it.

---

[1] Jour. Infect. Dis., 1916, 19, p. 260.

A better estimate of the degree of bacillemia in tuberculosis would be the examination of arterial blood and clots. Usually, however, the left ventricle and aorta are empty at autopsy, and the left auricle contains but a small amount of clot or blood. The problem can be approached, however, by the study of the bacillary content of the right heart in cases of miliary tuberculosis in which the primary focus is on the venous side of the circulation, as for instance in the cervical or mesenteric lymph nodes. We have recently had in this laboratory such a case, with primary tuberculosis of the cervical lymph nodes and an even more widely disseminated miliary tuberculosis (skin, endocardium) than in Wilson's case, with lesions in the same early stage. The case was one of chronic lymphatic-myelogenous leukemia with secondary tuberculosis.

THE CASE

A stationary engineer, aged 50 years, entered the clinic with a history of progressive enlargement of cervical lymph glands. On Sept. 10, 1915, an enlarged cervical gland was removed and sent to this laboratory for pathologic examination. Sections showed a lymphoid (aleukemic) hyperplasia strewn with young epithelioid noncaseating tubercles. During his stay in the hospital, up to his death on Oct. 11, 1915, a rapidly increasing number of white cells in the blood was observed; so that the final clinical diagnosis was given as acute miliary tuberculosis with acute leukemia.

The pathological diagnosis follows: Chronic lymphatic (mixed lymphatic-myelogenous) leukemia; primary tuberculosis of cervical glands; acute miliary tuberculosis of all organs, including skin; endocardial tubercles; multiple lymphomata of kidneys and liver; leukemic infiltrations of gallbladder and intestine; Roentgen-ray pigmentation of skin and atrophy of testes; chronic parenchymatous nephritis; chronic catarrhal gastritis; bronchopneumonia.

The marked lymphoid hyperplasia of lymph glands, particularly the cervical, the thickening of the capsule, the hyperplasia of the stroma and the periglandular infiltrations, the hyperplasia of the spleen and the bone marrow, the presence of lymphomata and leukemic infiltrations throughout the body—all indicate a chronic leukemic process. The early stage of the tuberculous lesions shows a later secondary infection beginning in the cervical glands and thence spreading by both hematogenous and lymphogenous metastases throughout the body. The small number of leukocytes in the circulating blood when the patient was first examined, could be explained as the result of a decrease caused by acute tuberculous infection (aleukemic stage). The increase in the number of leukocytes observed during the patient's stay in the hospital may be interpreted as a change from the aleukemic to the former leukemic condition, induced by the acute infection.

The right auricle and ventricle were dilated and partly filled with soft leukemic clots (chicken-fat clots), 90 c.c. in amount in all. Sixty cubic centimeters of the clot were fixed in alcohol and 30 c.c. in formol. A portion of the alcohol-fixed clot, measuring 9 by 6 by 0.45 mm. (24.3 c.mm.), was imbedded in paraffin, and cut into 60 sections, 7.5 microns each in thickness. These sections were floated onto warm carbolfuchsin, stained, decolorized, and washed without removing the paraffin, then floated onto slides, dried, the paraffin removed by warming and applying xylol, and the sections finally mounted in balsam.

The 60 stained sections were thoroughly studied in all parts on a movable stage. Only absolutely typical and unquestioned tubercle bacilli were counted. The fact that the clots were leukemic, made up almost entirely of white cells, with but few red cells and these hemolyzed by the alcohol fixation, made the search for tubercle bacilli much easier than was the case in formol-fixed clots. By means of the movable stage one slide could be thoroughly examined in 1 hour; 60 full hours were given to the examination of the 60 slides. Four absolutely typical tubercle bacilli were found which by size, morphology, and staining were identified beyond question; also 15 suspicious fragments, which were disregarded. The sections were well stained, contained little dirt, and few acid-resisting crystalline structures were to be seen. The 4 bacilli were in the focal plane of the section between the white cells, and could not have been technical artefacts or acid-resisting bacilli from water or air. They must have existed in the blood clot at the time of its formation. The portion of clot examined represented 0.027% of the entire clot obtained from the heart. An estimate of the number of bacilli occurring in the entire clot, should this ratio of occurrence persist throughout, would give 14,815 bacilli for the entire clot. Such a calculation, however, does not sufficiently consider the laws of chance, and must not be too strongly heeded. The fact remains that in a case of acute miliary tuberculosis 4 tubercle bacilli to 60 slides, or 1 to 15, were found in the venous blood of the right heart. This proportion, which is not uncommon in sputum examinations in incipient cases of pulmonary tuberculosis, or in examinations of urinary sediments, is not considered insignificant as a clinical diagnostic effort in such conditions.

Tubercle bacillemia is a common, if not universal, occurrence in cases of tuberculosis. Can it be demonstrated in blood drawn from the living patient? Probably only by examination of many slides, a laborious undertaking, perhaps more laborious and time-consuming than the examination of sputum and urinary smears in cases of suspected incipient pulmonary and renal tuberculosis, but nevertheless worth while in many cases. The examination of blood taken from the living patient will probably give results more frequently in cases in which the primary focus is in the lungs or bronchial nodes; while in the cadaver the heart blood of the right side will contain more bacilli in those cases in which the primary lesion is giving off bacilli to the venous circulation. The report of Brandes[2] on the examination of blood from 40 cases of surgical tuberculosis with positive results in 45% of these cases (5 c.c. of blood treated by the Schnitter-Uhlenhuth antiformin method) strengthens the belief that the attempt may not be as difficult as it now seems. A suggested improvement consists in imbedding in paraffin the sediment obtained by the antiformin method (decantation method of paraffin imbedding, as for blood), and the examination of the stained sections rather than smears. Thus some of the technical artefacts would be avoided and labor saved.

---

[2] Deutsch. med. Wchnschr., 1913, 39, p. 1137.

Bacillemia in Tuberculosis as Shown by the Examination of Postmortem Clots from the Heart

UNITY FLETCHER WILSON

Reprinted from THE JOURNAL OF INFECTIOUS DISEASES
Vol. 19, No. 2, Aug. 1916, pp. 260-262

BACILLEMIA IN TUBERCULOSIS AS SHOWN BY THE EXAMINATION OF POSTMORTEM CLOTS FROM THE HEART

Unity Fletcher Wilson

From the Pathological Laboratory of the University of Michigan, Ann Arbor

A study of the literature on the subject of the presence of tubercle bacilli in the blood of tuberculous patients reveals much conflict both in opinion and in experimental evidence. That tubercle bacilli enter the blood vessels and are generalized by means of the circulating blood is of course unquestioned; but to what extent this generalization takes place is still unsettled. Is the bacillemia in tuberculosis continuous enough or so marked that it can be demonstrated and utilized as a means of diagnosis? Particularly in acute miliary tuberculosis are the bacilli likely to be found in the circulating blood; and the demonstration of their presence there would be of practical importance in the diagnosis of early doubtful cases. Most experimental evidence indicates, however, that at no time is the bacillemia sufficient to have any diagnostic worth.

The many attempts to demonstrate tubercle bacilli in blood smears have ranged in result from the extravagant claims of Rosenberger,[1] since shown to rest on technical error, to the almost universally negative findings at the hands of numerous workers. Efforts to obtain the bacilli from the blood by culture or by animal inoculation have likewise given chiefly negative results. Bergeron[2] secured 3 positive cultures; and Faber[3] was successful in cultivating the organisms from blood taken at autopsy in 1 case of miliary tuberculosis. Recent investigators (Berry,[4] Kessel[5]) have also failed to demonstrate the presence of tubercle bacilli in the blood of advanced cases of pulmonary tuberculosis, either by smears, culture directly from the blood, or by animal inoculations. Much more successful has been the demonstration of tubercle bacilli in the placental blood of placentas from mothers suffering either with acute miliary or chronic pulmonary tuberculosis (Norris[6] and others). The not infrequent occurrence of placental tuberculosis in cases of slight latent pulmonary tuberculosis of the mother (3 cases reported from this laboratory by Warthin[7] and Weller[8]) would tend to show the occasional entrance of tubercle bacilli into the blood stream from slight and apparently latent lesions, and that in pregnant women such bacilli are more likely to fall out of the circulation into the intervillous spaces of the placenta than in any other organ.

---

[1] Am. Jour. Med. Sc., 1909, 137, p. 267.

[2] Presse méd., 1905, 13, p. 129.

[3] Jour. Am. Med. Assn., 1914, 63, pp. 1656-1658.

[4] Jour. Infect. Dis., 1914, 14, p. 162.

[5] Am. Jour. Med. Sc., 1915, 150, p. 277.

[6] Tr. Am. Gynec. Soc., 1914, 39, p. 452.

[7] Jour. Am. Med. Assn., 1913, 61, p. 1951

[8] Arch. Int. Med., 1916, 17, p. 509.

One other method of determining the presence of tubercle bacilli in the blood after death, not yet reported in the literature on tubercle bacillemia, is the examination of the postmortem clots in the heart and great vessels by means of stained sections. This method would at least give a definite idea of the number of tubercle bacilli in the heart blood at time of death. At Dr. Warthin's suggestion I have attempted to make such an estimation on blood clots from the heart in a case of generalized miliary tuberculosis in which the dissemination was extreme and the tubercles relatively young.[9]

THE CASE

A housewife, aged 52 years, with negative family history as regards tuberculosis, became ill about Oct. 21, 1914, with a feeling of unusual fatigue, fever and slight chilly sensations, increasing toxemia, rapidly progressing anemia, weakness, and dyspnea, without any signs of localized disease. Death took place on Nov. 29.

The gross and microscopic examinations at the autopsy furnished the following pathologic diagnosis: Primary tuberculosis of bronchial nodes with secondary pyogenic infection; cold abscesses in bronchial nodes with rupture into pulmonary vein; healed tubercle in right lung; miliary focal tuberculous necroses in lungs, liver, spleen, and bone marrow; older miliary tubercles in kidney; colonies of tubercle bacilli in myocardium; multiple thromboses (tuberculous) in pulmonary veins, portal vein, and ovarian plexus; exhaustion of bone marrow; secondary anemia; gravis aplastica; fatty degeneration of heart and liver; chronic fibroid salpingitis. Tubercle bacilli in large colonies in the focal necroses.

If tubercle bacilli ever exist in the circulating blood in large numbers, this case would seem to be favorable to such a condition, because of the early stage of the tubercles, the lesion opening into a pulmonary vein, the wide dissemination of the lesions, and the apparently progressive entrance of bacilli into the circulation as shown by the varied picture of the tuberculous foci ranging from thromboses, coagulation and caseation focal necroses, to fully developed epithelioid tubercles.

The white clots and blood found in the right side of the heart were fixed in mercuric chlorid, carefully washed, and imbedded in paraffin. The sections were floated onto warm carbolfuchsin without removal of the paraffin, decolorized, and counterstained with methylene blue, washed, dried on the slide, the paraffin removed by warming and the use of xylol, and the sections mounted in balsam. These stained sections were then carefully searched for tubercle bacilli. In all, about one-tenth of the entire mass of clot and blood obtained from the heart (chiefly white clots from the right auricle) was examined in this manner. Only 4 typical slender and beaded acidfast bacilli were found in the blood-clot sections. Sections of the tuberculous lesions in the organs stained in the same manner showed the presence of similar acidfast bacilli in enormous numbers in the focal necroses.

---

[9] [illegible]: Arch. Int. Med., 1915, 16, p. 1017.

If the other nine-tenths of the heart blood and clot not examined contained tubercle bacilli in the same proportion as the one-tenth examined, then the entire number contained in the heart blood at time of death would be 40 or less. In this case, as the disease was in a most acute and severe form and the organisms were being generalized throughout the body in large numbers, the number of bacilli found in the blood at any given moment would have to be relatively small, and the chances for demonstrating their presence by stained smears, cultures, or animal inoculation could not be very favorable. In milder cases, and in cases of chronic pulmonary tuberculosis, the chances for such a diagnostic demonstration of the bacilli in the circulating blood would seem to be very small indeed.

CYLINDROMA OF THE TONGUE

With a Report of two Cases

By ROBERT H. BAKER, A.B., Ann Arbor, Michigan
Staff Assistant in Pathology, Pathological Laboratory, University of Michigan

Reprint from
SURGERY, GYNECOLOGY AND OBSTETRICS
September, 1916, pages 356-360

CYLINDROMA OF THE TONGUE

With a Report of Two Cases

By ROBERT H. BAKER, A.B., Ann Arbor, Michigan
Staff Assistant in Pathology, Pathological Laboratory, University of Michigan

CYLINDROMA, characterized by hyaline formations of typical arrangement, has been described in the textbooks as having the following clinical characteristics: It is located about the head, especially about the orbit, the salivary glands, nose, antrum of Highmore, and the mucous membranes of the cheek and gums. Its growth is slow, recurrences are frequent, but there are no metastases. Except for some forms described that seem to include a distinctly sarcomatous element, the tumor seems to be relatively benign. Some confusion exists from the fact that some quite different tumor forms have displayed some of the same hyaline characteristics, and also because of the lack of agreement in defining the term cylindroma and endothelioma.

Several cases that may be described under the title cylindroma have been discussed in the literature. In general the majority of observers have classed the growth as an endothelial form of connective-tissue tumor. Some difference of opinion exists even on this point, some men choosing to explain the hyaline structure to be described later as a product of mature connective-tissue elements. Others like Lubarsch (1) believe the form originates, not from the endothelial but from the perithelial cells of the blood and lymph-vessels. The most widely held opinion is, however, that the tumor is an overgrowth of endothelium lining lymph and blood-vessels, and that the hyaline so generally described is either a degeneration product or a secretion product of these cells. This latter point has not been so widely discussed.

In 1912, Dr. Oberlin (2), in a concise and thorough review of the cylindroma question, reported three cases from this laboratory which she described as cylindromata. In that report she considered all the literature to date stating the prevailing theories of origin, development, and classification of this relatively rare form. Two of the three cases which she reports came from the head with a history of 15 to 30 years growth. These she describes as endotheliomata. The third case from the uterus, of rapid growth, exhibits a mixed type with a sarcomatous element. In 1914, Baumgartner (3) in discussing "*la pathogenie du cylindrome*," takes this view: that the cylindroma is a mixed tumor consisting of epithelial and mucoid elements existing side by side and with a predominance of the mucoid material. A further discussion of his views will be considered later in this report.

The especial interest attached to the two cases in hand is the fact that in all cases described in the literature to date, none has been mentioned as coming from the tongue. Both tumors were received at the Pathological Laboratory of the University of Michigan within a period of less than two months and present nearly identical features.

Case 1 (4) must be discussed only in the light of its microscopical appearance as no history was obtainable. Case 2 (5) occurred in a woman, age 30. Two years previous it began as a thickening on the right dorsum of the tongue. It grew slowly until about three months before removal at which time it became painful and grew more rapidly. No adenopathy occurred with the growth and it was removed entire with its capsule.

In the gross, Case 1 appeared somewhat bilobed with a dimension of about eight millimeters in its two smaller diameters and twelve in its greatest dimension. Case 2 was somewhat larger and existed as a single mass. Neither of the tumors was received in fresh enough state to express the hyaline tubes as has been described by some authors. Both tumors gave the hyaline glassy appearance usually described in the section of such growths, the descriptive name cylindroma coming obviously from the appearance of the outline cylinders and balls on section in the gross.

Microscopically, the specimens present the following features: Enclosed within a thin but quite definite connective-tissue capsule within the muscle of the tongue, is to be seen the characteristic arrangement of curved and twisted hyaline strands, which, in serial section would form the cylinders and knobs described in the gross. In some parts of the tumor the hyaline patches are seen to include small nests and cords of cells which appear to be of the endothelial type—flat with rounded and ellipsoidal nucleii containing in some, apparently the most recently formed cells, a rather limited amount of chromatin material. These cells vary quite markedly in size, averaging somewhat larger than the endothelial cells lining normal lymph spaces. The same type of cells is noticed in greater abundance arranged in nests and cords extending between the hyaline cylinders. The somewhat radial arrangement of these cells in reference to the hyaline cords is due, I believe, to contraction of this latter substance. A noteworthy feature is that the hyaline areas are almost exclusively bounded by these cells, suggesting the origin of the hyaline. A much less conspicuous element is the mature connective-tissue cell, which, with some small blood and lymph-vessels serves to make up the rest of the tumor. Special staining by Kresyl-Echt-Violett gives no staining reaction for amyloid or mucin. Van Gieson's stain gives the deep rose-red reaction characteristic of connective-tissue hyaline to the non-cellular glassy, material, and no reaction for mucin is obtainable.

Under higher magnification, certain quite distinct markings within the hyaline material suggest the outline of large flat cells from which the nucleus has degenerated. This conception is further substantiated by finding here and there a definite cell inclusion within the hyaline, showing the complete cell outline but with the space vacuolated and a contracted pyknotic nucleus at one side. By careful search such cells are seen in all stages of disintegration, even to the point where the nucleus has lost its contour and only a remnant of chromatin remains within a cell boundary. This same cell may show an imperfect wall and may enclose what appears to be a beginning infiltration with the hyaline which I assume to be a secretion of this or other cells about it.

The connective-tissue elements in both the tumors at hand show a marked hyaline degeneration, but it is quite impossible to trace the relation of this tissue to the hyaline of the cords. The tumors show some small blood vessels with markedly sclerotic walls while others farther removed from the hyaline cylinders are quite normal in appearance. One of these tumors presents a somewhat different picture *en masse* than the other, a difference which I interpret as representing a younger stage of the growth of this peculiar tumor form.

In the first case one is struck by the profuse vascularity of the growth, the conspicuous element being the large number of dilated lymph and blood-capillaries and spaces. The ramification of the capillaries is easily made out as they stand out sharply, often containing a line of red blood-cells. The hyaline cords are not in this case so large or so definitely circumscribed as will be described in Case 2. The connective-tissue elements are much less conspicuous, as they are so scattered among the lymph-spaces, and have not, in this younger stage of the tumor, undergone the same degree of sclerosis and hyaline change, which is so much more evident in the second case as a result of the restriction of blood and lymph supply. One is impressed, however, by what seems to be a significant fact. In certain areas where the sections show most clearly the curling and branching of capillaries in a single plane, one can see between the unbroken endothelium and the connective tissue which makes up the framework of the tumor, small areas of the hyaline which from its very relation suggests that it is a secretion product of the endothelium. Where the massing of this material is more marked one sees that the lumen of the spaces is correspondingly restricted until we have in some fields the small cell inclusions referred to above. This peripheral distribution of hyaline I believe to be but a chance one as in other fields one is equally attracted by the fact that the hyaline strands are definitely included within a single line of endothelium and contain no cell inclusions, the hyaline substance here being quite certainly a secretion within the lumen of the capillaries.

In the second case, one is struck by a more characteristic appearance of the hyaline tubes. Here we have the same cellular elements as described above, but in somewhat altered proportion and arrangement of these. There are seen definite trabeculæ of connective tissue to form a framework, including capillaries of large caliber. Both these factors are markedly sclerotic. Within the enclosure of these trabeculæ is seen the much twisted and whirl-like arrangement of the hyaline cords. The structure here is not essentially different from that in Case 1, but we notice a relative lack of connective tissue fibers and of capillaries and lymph spaces seen above. But here the hyaline cords are larger and do not show the earlier stages of cell degeneration. The distribution of hyaline, too, is generally one of secretion within the lumen as evidenced by the external lining which these cords show.

The interpretation to be made then from these observations is this:

1. That the tumors in question arise from abnormal proliferation of blood and lymph capillaries and spaces.

2. That the endothelial lining of these capillaries and spaces gives rise to a secretion of some material which gives the staining reaction of connective tissue hyaline.

3. That this hyaline substance receives a chance distribution centrally or peripherally to the secreting cells.

4. That the excessive proliferation of the vascular elements meeting the resistance of the firmer connective-tissue framework and of the increasing resistance of the hyaline material, tends to assume a much twisted, curling, convoluted structure.

5. That the increasing tension within these convolutions from proliferation and excessive hyaline formation, causes first a shutting off of the vascular supply to the tissue and ultimate necrosis of the endothelial cells and tends also to restrict the nutrition of the connective-tissue elements with resulting sclerosis and hyaline degeneration.

That the tumors are not of connective-tissue origin, I think is proved in that they quite clearly are associated with endothelial structures and in all stages show no relation to the connective-tissue elements they enclose. Any degeneration of connective-tissue stroma which may be demonstrable in these tumors, I believe to be but secondary to a primary change in the endothelium in contradistinction to the view of Ewetsky (6).

That the hyaline secretion is not perithelial in origin as Lubarsch states, I believe to be evidenced by the fact that these hyaline inclusions are seen to be within an endothelial boundary in the greater part of the growth.

Baumgartner, following the view of Malassez, thinks the cells composing the main part of this form to be epithelial. He further thinks these cells exist in conjunction with a mucoid substance. The preponderance of this latter element he explains as due to the greater vitality of the mucin over the epithelium. He further explains the growth as centrifugal in its course. That the cells are epithelial he attempts to prove by the fact that they do not seem to him to have any connection with the blood-vessels. He describes them as being atypical in the center, but showing the characteristics of cuboidal and columnar cells at the periphery of his sections. They do not show signs of being secretory so therefore he concludes that the mucoid substance is not a secretion of these cells, nor is this substance a degeneration or a vegetative development of these cells. By staining reactions he is satisfied that the material is not myxomatous but true epithelial mucin in nature. In a review of 400 cases described as cylindroma he chooses 83 as true to the type. Seventy-four of these are described from the head, three from the sacral region. He explains the presence of mucoid tissue as an embryonic remains similar to the vitreous of the eye, and cites the existence of 23 cases from the orbit to substantiate this relation. The description of cylindroma-like areas in teratoids lends further weight to his theory of the embryonic origin of this substance. That the epithelial relation of the cells in these tumors is not valid, I can only combat with the evidence which I have offered.

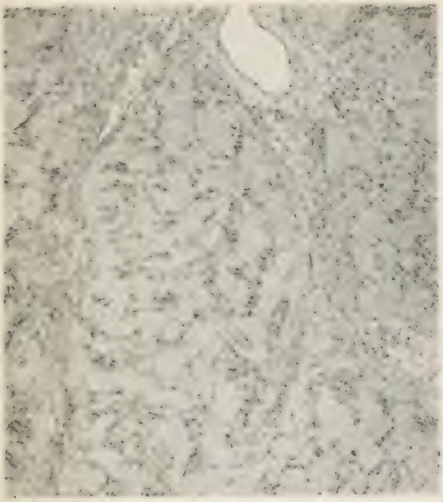

Fig. 1. Cylindroma of the tongue (low power), showing characteristic appearance of the endothelial cell cords and nests and the hyaline cylinders and knobs

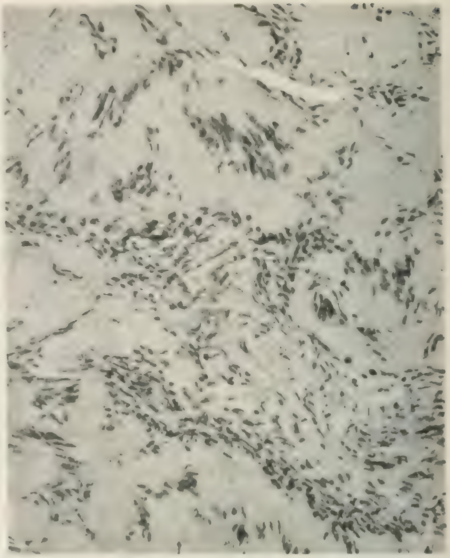

Fig. [illegible]. Cylindroma of the tongue (high power), showing the relation of connective tissue stroma to the endothelial cells and hyaline tubes, and the intimate relation of the hyaline to the endothelium of capillaries and lymph-spaces.

Moreover, following the analogy of this mucoid substance with the vitreous we must look for a cell-matrix which will be the origin of this mucin just as the vitreous takes its origin in the epithelium of the posterior zone of the ciliary body. That the substance is not mucin is certain in these two cases and that it is a secretion of the cells seems a logical conclusion though the secretory power of these cells cannot be proved. The underlying idea of Baumgartner and others that these tumors are possibly embryonic in origin and assume a development during extra-uterine life, is a conception which seems quite tenable.

That the cylindroma may be described fitly as a tumor entity, I believe is justifiable because of the fact that several of the cases described under this title have shown no clinical or pathological relation to either carcinomata, sarcomata, or enchondromata, as believed to be the case by Foerster (7), R. Volkmann (8), and R. Maier (9). A recent report by Richard Weil (10) of a parotid tumor which he has considered as an example of cylindroma, gives evidence of the frequently mistaken identity of this tumor form. The clinical history of his tumor might fall well within the limits of the cylindroma, but his brief discussion of its histological nature and his photomicrograph certainly do not conform to the type of tumor I am describing as cylindroma. It is undoubtedly such degenerative forms of epitheliomata that have so complicated the exact classification of the cylindroma. Cylindroma is a descriptive term. But the cell of the cylindroma does not partake in character or arrangement of the features of the basal cell. Dr. Oberlin's Case 3, from the uterus, is also an example of a malignant growth with degenerative areas of the nature of cylindroma. Such cases should, I believe, be called sarcoma cylindromatosum to express this resemblance to cylindroma. True cylindromata show few degenerative changes, in some cases mucin being demonstrable. On the contrary, they seem relatively benign and evidence microscopically only the arrangement and elements described above.

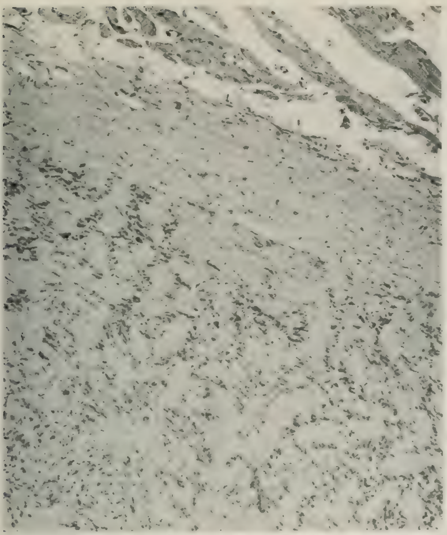

Fig. 3. Cylindroma of the tongue. The dense connective-tissue capsule is shown enclosing the tumor and separating it from the tongue muscle.

The exact nature and origin of the cylindroma which will lead to its final classification among tumors must remain undecided. I believe, however, that the evidence submitted in my cases combined with that of similar reports, points to a logical conclusion. In the belief that the endothelium may take part in the formation of sarcomata, the cylindroma should be considered as a variable form of sarcoma, according to Borst (11). True cylindroma is not clinically or microscopically of the character of sarcoma, however. The tissue is not sarcomatous and not infiltrating, but is sharply circumscribed by a connective-tissue capsule. If then we consider this form as essentially endotheliomatous, in what does it take its origin? From the cases of true cylindroma described in the literature, we are struck by the benignity of the form. The clinical history usually is that of a slow growing nodule lasting over a period of years. The one history which I submit may seem to indicate an exception to this statement. We cannot be certain, however, that the history of more rapid growth in the last three months, is not due, in this case, to some degree of inflammatory infiltration due to the mechanical irritation of the tumor proper. Considering then the long history, the benignity, and the simplicity of the tumor-element — a connective-tissue hyaline on a base of capillaries — it seems logical from pathological experience, to consider this of the nature of angioma, simplex or perhaps hypertrophicum. In this event cylindroma may be described as of embryological origin, of a type of angioma, assuming its clinical characters usually some time in adult life. The hyaline may be believed in this case to represent some sort of an attempt on the part of the body at a reparative process in the existing angioma.

Further evidence as to the duration of growth, location, clinical manifestations, and microscopical characters, in young forms alone, can give this tumor its definite place in the classification of tumors. Until then it may quite logically be considered under the title of cylindroma, endothelioma cylindromatosum, or angioma cylindromatosum.

I desire to express my gratitude to Drs. Warthin and Weller for valuable assistance and advice in making this report.

REFERENCES

1. Hyperplasie und Geschwuelste. Ergebn. d. allg. Path. u. path. Anat., p. 368.
2. Cylindroma. Physician & Surg., 1912, May.
3. La pathogenie du cylindrome. J. de path. et physiol., Paris, 1914, xvi, 451.
4. Case 1589S, referred by Dr. R. E. Skeel, Cleveland. Ohio.
5. Case 1283S, referred by Dr. William Veenboer, Grand Rapids, Mich.
6. Zur Cylindromefrage. Arch. f. path. Anat., lxix.
7. Atlas der mikroskopischen pathologischen Histologie, p. 47, fig. xxx.
8. Arch. f. path. Anat., xii, 293.
9. Arch. f. path. Anat., xiv, 270.
10. Treatment of parotid tumors by radium. J. Am. M. Ass., lxv, No. 25.
11. Einteilung der Sarkome. Beitr. z. path. Anat. u. z. allg. Path., 1906, xxxix, 528.

The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or "Cured" Syphilis

BY

ALDRED SCOTT WARTHIN, Ph.D., M.D.
PROFESSOR OF PATHOLOGY AND DIRECTOR OF THE PATHOLOGICAL LABORATORIES IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR

FROM THE
AMERICAN JOURNAL OF THE MEDICAL SCIENCES
October, 1916, No. 4, vol. clii, p. 508

Extracted from the American Journal of the Medical Sciences,
October, 1916, No. 4, vol. clii, p. 508.

THE PERSISTENCE OF ACTIVE LESIONS AND SPIROCHETES IN THE TISSUES OF CLINICALLY INACTIVE OR "CURED" SYPHILIS.

By Aldred Scott Warthin, Ph.D., M.D.,
PROFESSOR OF PATHOLOGY AND DIRECTOR OF THE PATHOLOGICAL LABORATORIES IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR.

(From the Pathological Laboratory of the University of Michigan.)

Between the pathologist and the clinician there is always a certain antagonism of attitude with reference to the curability of any given disease. The clinician is, and naturally must be, more or less optimistic as to the results of therapy; and only with the greatest reluctance is he convinced of the weakness or total failure of his therapeutic means and methods. The pathologist, with the opportunities afforded him by tissue examination and autopsy, has the advantage of the very last word; and he becomes pessimistic as to ultimate cure because of his constantly recurring experience of finding evidences of active disease in cases clinically cured. This clash of opinion, clinical and pathological, is not shown elsewhere to such a degree as in the case of the veneral diseases, gonorrhea and syphilis. It took much work on the part of the pathologist to convince the practitioner that clinically cured cases of the so-called "lesser disease" were only apparent cures, and that the gonorrhea-infected individual remained for an indefinite period a germ-carrier, not only dangerous to himself but much more so to his future sex-partner. Likewise in the case of syphilis, therapeutic optimism has in recent years received severe blows at the hands of the pathologist. The frequency of latent syphilis of the heart, aorta, and central nervous system, the demonstration of spirochetes in conditions (paresis, tabes, etc.) until very recently regarded as parasyphilitic in nature and etiology, thus proving these conditions to be still active infections, have somewhat shaken clinical optimism. Cures once promised after a year of active treatment have passed through the two-, three-, and five-year limit, and now some clinicians are advising the syphilitic to take interval treatment over a period of many years or even throughout his lifetime if he will escape the uncertain chances facing everyone who acquires this disease. The wave of therapeutic optimism excited by salvarsan and the negative Wassermann reaction even now is subsiding.

It has been my experience as a pathologist to become very pessimistic as to the curative effects of any of the present-day methods of treating syphilis. Before the spirochete became an absolute pathognostic sign of the presence of this disease, certain myocardial, aortic, and testicular changes were regarded by the pathologist as well-nigh positive proof of syphilis. The practically constant occurrence of these changes in the bodies of cases of clinically cured syphilis gave the pathologist good reason to believe that he was dealing with a still active process, although he had no means of proving this. The pathologist's judgment of these conditions is now confirmed by the demonstration of the spirochete of syphilis in such lesions. Localized tissue lesions of the smallest size and of the simplest nature (fatty degeneration, edema, etc.), that, a few years ago, would not, by any possibility, have been regarded as syphilitic, have been shown to be evidences of the local presence of spirochetes. I have elsewhere urged the fact that our conceptions of syphilis, both pathological and clinical, must be reshaped in the light of the spirochete; and that much work needs to be carried out along this line. The methods for the demonstration of this organism in the tissues should be made a part of the routine autopsy microscopic examination.

In my laboratory we have used Levaditi's original method with great success, and this is at the present time the only method of any value in demonstrating the presence of spirochetes in tissue. Its success will depend in the first place upon the freshness of the tissues. In my experience the spirochetes of syphilis quickly disappear from body tissues after the body becomes cold. Our necessity of having to make autopsies very soon after death has been a very great advantage in this respect. Tissues taken from a warm body within one to two hours after death and immediately fixed in 10 per cent. formol for at least twenty-four hours (better for three days), then put through the Levaditi method and blocked in paraffin give the best results. A formalin neutral in reaction and that has not been kept in wooden casks should be used. When properly prepared the number of spirochetes at times demonstrable in the tissues of congenital and active acquired syphilis is incredibly large. In the case of old latent syphilis the search for the organisms often becomes a prolonged hunt, and much time may be consumed in finding active lesions and demonstrating spirochetes within them. No one should think that this is wholly an easy matter. With an autopsy service of fifty to sixty cases a year the time of one assistant may easily be taken wholly for this work, should histological lesions of syphilis be found only in one-third of these. Such an arrangement I have had temporarily, but even with this advantage, the work has gone slowly enough. It may, however, be greatly expedited by confining the work to the organs, heart, aorta, testicles, and adrenals, most commonly the site of latent syphilis, and by making control blocks of all parts of the organ or tissue for quick survey in ordinary hematoxylin and eosin staining. Should such control blocks show lesions recognizable as those possibly due to the localization of spirochetes, the corresponding block in Levaditi preparation is then examined first before a general examination of all the Levaditi blocks is made. If the blocks taken are small, as they should be, the neighboring Levaditi block is very likely to show some active process also. It may happen, however, that the hematoxylin and eosin sections alone show active lesions. The experiment of removing the paraffin and then putting the remaining portion of the block through Levaditi may be tried, but we have not found this procedure very satisfactory.

In the pathological service of the University of Michigan there were from 1912 to 1914, forty-one autopsy cases (one-third of the adult cases) that on microscopic examination showed active syphilis, determined either by the presence of the spirochetes or by characteristic tissue lesions. In the latter the spirochetes are being demonstrated as fast as the work can be carried out; and this has already been accomplished to such an extent in Class I, all cases in Class II, and in ten cases in Class III (one-half of the latent cases) as to leave no doubt of the correctness of the diagnosis in all of the cases. A preliminary report of this investigation was presented before the Association of American Physicians in 1914, and the publication of this paper has been delayed in the hope that we might be able to demonstrate the presence of spirochetes in all of the "cured" and unsuspected latent cases. This is only half completed. The labor has been much greater than at first anticipated. Six weeks were spent on the heart of one case before a small group of spirochetes was finally found. In eight cases in Class III, my assistant, Miss Wilson, demonstrated spirochetes in the heart muscle, but this work occupied a large part of a year.

The clinical history of a part of these cases gave no suspicion of the existence of a previous syphilitic infection; in others there was a doubtful or suspicious history of the disease; while in a smaller number the patient had been treated, or was at the time of death undergoing treatment, for syphilis. In the majority of cases, it will be seen, the clinical diagnosis, and consequently the treatment, entertained no suspicion of the existence of latent syphilis. In those cases in which syphilis was suspected or diagnosed the treatment in part had been regarded as adequate by the patient and previous physicians, but a new course of treatment had been instituted after coming to the hospital. In a small number of cases the treatment had been more modern; the use of salvarsan had been thoroughly carried out and the case regarded as clinically cured. As the taking of the Wassermann reaction has been made only during the last year a part of the regular examination routine for our hospital cases, it was made in the case of only a small number of those in whom syphilis was unsuspected. In the case of those in whom the infection was suspected or diagnosed it was regularly made. Notes concerning the Wassermann are given with each case.

I have accordingly divided the forty-one cases into three classes: (1) cases in which there was a known history of syphilis, with treatment regarded as adequate and resulting in a cure; (2) cases in which the syphilitic infection was recognized as still active, treatment being continued; (3) cases in which a syphilitic history could not be obtained or was specifically denied by the patient, the clinical diagnosis not including syphilis and no antisyphilitic treatment given.

CLASS I.—CASES WITH A HISTORY OF RECOGNIZED SYPHILIS, TREATMENT, AND CLINICAL CURE.

1. Case C.—Age, sixty-two years. Chancre when a young man; treated by physician; never any other symptoms of the disease; apparent cure. No history of alcoholism. Wassermann not made. Clinical diagnosis of enlarged prostate. Operation. Death.

Pathological Diagnosis. Postoperative infection. Chronic purulent pyelonephritis. Old syphilis. Healed gummata of liver and testis. Orchitis chronica fibrosa syphilitica. Chronic epididymitis. Emphysema. Active syphilis in myocardium and aorta.

2. Case M.—Age, sixty-three years. "Cured syphilis." No symptoms since chancre when a young man. Clinical diagnosis of peritonitis following operation on bladder. No Wassermann.

Pathological Diagnosis. Postoperative peritonitis. Chronic cystitis. Papilloma of bladder. Chronic prostatitis and vesiculitis. Fatty degeneration of all organs. Bronchopneumonia. Latent syphilis in myocardium, aorta and testes.

3. Case F.—Age, sixty-four years. No history of infection. Treated with mercury. "Cured." Blood gave a positive, and cerebrospinal fluid a negative Wassermann. Clinical symptoms cardiac. Question of aortic aneurism.

Pathological Diagnosis. Mitral insufficiency and stenosis. Aortic insufficiency. Relative tricuspid insufficiency. Chronic parenchymatous nephritis. General atherosclerosis. Chronic passive congestion of all organs. Healed infarcts in lungs and kidneys. Thrombosis. Latent syphilis of heart and testes.

4. Case K.—Age, forty-nine years (?). Sudden death following fracture of bones of leg. "Cured" syphilis when a young man. Chronic drinker. No Wassermann. Clinical diagnosis of embolism.

Pathological Diagnosis. Fracture of right tibia and fibula. Thrombosis of veins of right leg. Embolus in left pulmonary artery. Fat embolism of lungs. Early stage of alcoholic cirrhosis. Active syphilis in heart and aorta. Advanced syphilitic fibroid orchitis.

5. CASE S.—Age, forty-five years. Chancre when young. Treated. Later tertiary recurrence. Treatment resumed. "Cured." Drinker. No Wassermann. Committed suicide with carbolic acid.

Pathological Diagnosis. Carbolic acid poisoning. Latent syphilis. Saddle-nose. Gumma of spleen. Active syphilis of heart, aorta, adrenals, and testicles. Advanced orchitis syphilitica fibrosa.

6. CASE M.—Age, seventy years. Syphilis when a young man. "Cured." Chronic drinker. Clinical diagnosis of uremia. No Wassermann.

Pathological Diagnosis. Chronic parenchymatous nephritis. Chronic prostatitis, vesiculitis, pyelitis, and cystitis. Localized chronic leptomeningitis. Coronary sclerosis. Hypernephroma of right kidney. Active syphilis in aorta, myocardium and testicles.

7. CASE R.—Age, fifty-nine years. Date of infection not known. Treated. "Cured." No history of alcoholism. Wassermann negative. No clinical symptoms of syphilis. Clinical diagnosis of tumor of kidney.

Pathological Diagnosis. Hypernephroma of right kidney. Chronic parenchymatous nephritis, prostatitis, vesiculitis, and cystitis. Old tubercles in bronchial nodes. Gummata of spleen and liver. Active syphilis of myocardium, aorta, spleen, liver, and testes.

8. CASE L.—Age (?). Syphilitic infection twenty-three years ago. Treated with mercurials. "Cured." Chronic alcoholism. Died of croupous pneumonia. Both blood and cerebrospinal fluid gave a negative Wassermann.

Pathological Diagnosis. Croupous pneumonia. Syphilitic hepatitis. Syphilis of the aorta, heart, adrenals, and testes.

9. CASE MRS. J.—Age, (?) Time of infection unknown. No clinical signs of syphilis. Blood and cerebrospinal fluid gave negative Wassermann. Diagnosis of nephritis.

Pathological Diagnosis. Chronic parenchymatous nephritis. Syphilitic aortitis. Fibroid heart. Chronic cystitis. Emphysema. Chronic vaginitis.

10. CASE F.—Age, fifty-four years. Chancre at fifteen years of age. Treated. Never any other symptoms. Moderate drinker. Wassermann negative. Carcinoma of rectum.

Pathological Diagnosis. Adenocarcinoma of rectum. Secondaries in pelvis and peritoneum. General cachexia. Amyloid spleen. Syphilitic contracted kidney. Active syphilis of heart, aorta, and testes.

11. CASE G.—Age, forty-five years. Chancre twelve years ago. Treated. "Cured." Wassermann negative. Clinical diagnosis of chronic valvular disease.

Pathological Diagnosis. Aortic insufficiency. Aneurism of ascending aorta. Active syphilitic lesions in heart, aorta, and testes.

CLASS II.—CASES OF CLINICALLY ACTIVE SYPHILIS.

12. CASE W.—Age (?). Date of infection unknown. Blood and spinal fluid gave positive Wassermann. Under treatment for syphilis of central nervous system. Died of pneumonia.

Pathological Diagnosis. Acute purulent bronchopneumonia. Active syphilitic aortitis and meningoencephalitis. Fatty liver and heart. General marasmus.

13. CASE T.—Age, forty-seven years. Denied syphilitic infection. Symptoms of tabes. No history of alcoholism. No Wassermann. Under antisyphilitic treatment.

Pathological Diagnosis. Aictve syphilitic leptomeningitis. Miliary gummata in cord and brain. Diffuse degeneration and sclerosis of cord and brain. Chronic parenchymatous nephritis. Active syphilitic lesions in heart and aorta. Orchitis syphilitica fibrosa.

14. CASE H.—Age, forty-four years. Physician. Accidental infection nine years previously. Blood and spinal fluid gave positive Wassermann. Under active treatment. Early stage of paresis.

Pathological Diagnosis. Syphilis. Paresis. Acute purulent pneumonia. Subacute parenchymatous nephritis. Acute purulent pyelitis. Chronic cystitis. General atherosclerosis. Active syphilitic lesions in brain, cord, heart, aorta, liver, adrenals, and testicles.

15. CASE W.—Age, forty-four years. Had hard chancre when twenty-one years old. Secondaries. Treated. Now shows early stage of tabes. Wassermann positive. Under active treatment.

Pathological Diagnosis. Syphilis. Tabes. Active syphilitic lesions in brain, cord, heart, aorta, liver, and testicles. Acute parenchymatous nephritis. Chronic cystitis, vesiculitis, and prostatitis. Healed tuberculosis of bronchial nodes.

16. CASE S.—Age, forty-five years. Chancre fourteen years ago. Now symptoms of tabes. Wassermann positive. Salvarsan by intraspinal injections. Arsenical poisoning.

Pathological Diagnosis. Syphilis of brain, cord, heart, aorta, pancreas, and testes. Chronic interstitial nephritis.

CLASS III.—SYPHILIS DENIED OR NOT SUSPECTED CLINICALLY.

17. CASE G.—Age, sixty-three years. Denied venereal disease. No history of symptoms of syphilis. No Wassermann. No alcoholism. Clinical diagnosis of prostatic enlargement. Operation.

Pathological Diagnosis. Croupous pneumonia. Early stage of meningitis. Hypertrophy and dilatation of heart. Arteriosclerosis. Chronic parenchymatous nephritis and pyelitis. Chronic cystitis and prostatitis. Syphilitic lesions in heart, aorta, and testes.

18. Case D.—Age, sixty years. No history of syphilis. No Wassermann. Clinical diagnosis cancer of stomach.

Pathological Diagnosis. Colloid carcinoma of pylorus. Chronic parenchymatous nephritis. Arteriosclerosis. Syphilitic lesions in heart, aorta, adrenals, and testes.

19. Case Mrs. C.—Age, forty-five years. No history of syphilis. No Wassermann. Clinical diagnosis cystadenoma of ovary.

Pathological Diagnosis. Cystadenocarcinoma of ovary. Metastases in liver, spleen, and regional lymph nodes. Syphilitic lesions in heart and pancreas.

20. Case Co.—Age, forty-three years. No history of syphilis or alcoholism. No Wassermann. Clinical diagnosis of tumor of intestines.

Pathological Diagnosis. Primary lymphosarcoma of intestine. Secondaries in mesenteric and retroperitoneal lymph nodes, kidney, and liver. Chronic parenchymatous nephritis. Fatty cirrhosis of liver. Syphilis of heart, aorta, pancreas and testes.

21. Case S.—Age, sixty-eight years. No history of syphilis. No Wassermann. No history of alcoholism. Clinical diagnosis of carcinoma of stomach and senility.

Pathological Diagnosis. Active syphilis of brain, cord, heart, aorta, and testes. Early stage of paresis and tabes. Chronic prostatitis. Chronic parenchymatous nephritis.

22. Case Mrs. S.—No history of syphilis. No Wassermann. Dementia.

Pathological Diagnosis. Bronchopneumonia. Syphilis of heart and aorta. Coronary sclerosis. Fibroid heart. Biliary calculi. Adenomatous polyp of uterus.

23. Case Y.—Age, sixty-six years. Syphilis denied. No history of symptoms. No alcoholism. No Wassermann. Clinical diagnosis of myocardial insufficiency and coronary sclerosis.

Pathological Diagnosis. Active syphilitic myocarditis with cardiac thrombosis. Syphilitic aortitis. Multiple infarction of lungs and kidneys. Chronic parenchymatous nephritis. Early stage of cirrhosis of liver. Syphilitic lesions in adrenals and testicles. Chronic prostatitis, cystitis, vesiculitis, and pyelitis.

24. Case Mrs. Wa.—Age (?). Doubtful history of syphilis. Never pregnant. Negative Wassermann. Clinical diagnosis of carcinoma of uterus. Death after operation.

Pathological Diagnosis. Carcinoma of uterus. Recurrence. Postoperative sepsis. Acute parenchymatous nephritis. Syphilitic lesions in heart and liver. Glissonian cirrhosis.

25. CASE MRS. B.—Age, twenty-four years. Treated by previous physician for syphilis. Syphilis excluded in hospital examination. Wassermann negative. Clinical diagnosis of chronic valvular lesions.

Pathological Diagnosis. Active late syphilis. Chronic syphilitic myocarditis and aortitis. Combined stenosis and insufficiency of mitral, aortic, and tricuspid valves. Subacute parenchymatous nephritis. Multiple infarcts of lungs and kidneys. Severe anemia. Fatty liver. Syphilitic ulcer of leg. Gangrenous stomatitis, syphilitic with secondary infection. Colloid goitre.

26. CASE M.—Age, fifty years. No history of syphilis. Negative Wassermann. Clinical diagnosis of thoracic aneurysm and carcinoma of stomach.

Pathological Diagnosis. Carcinoma of stomach. Syphilitic lesions in heart, aorta, and testes.

27. CASE K.—Age (?). Denied venereal disease. Moderate drinker. Negative Wassermann. Enlarged prostate.

Pathological Diagnosis. Medullary carcinoma of prostate. Generalized metastasis. Addison's disease. Hydrothorax. Syphilis of heart, aorta and testes. Subacute parenchymatous nephritis. Chronic catarrhal gastritis. Hydrocele.

28. CASE MC.—Age, forty-four years. No history. Entered in toxic state. Suspected arsenical poisoning. No Wassermann.

Pathological Diagnosis. Acute alcoholic intoxication. Chronic alcoholism. Early stage of fatty cirrhosis of liver. Chronic parenchymatous nephritis. General atherosclerosis. Chronic pachymeningitis. Syphilis of testes.

29. CASE G.—Age, thirty years. Denied venereal disease. Negative Wassermann. Moderate drinker. Clinical diagnosis of chloroma.

Pathological Diagnosis. Primary carcinoma of pancreas; metastases in vertebræ, retroperitoneal glands, mesentery, adrenals, testes, and bronchial nodes. Syphilis of testes.

30. CASE MRS. B.—Age (?). No history or symptoms of syphilis. Wassermann negative on blood, 4+ positive on spinal fluid. Eight months pregnant. Clinical diagnosis of tuberculous meningitis. Miscarriage. Dead fetus.

Pathological Diagnosis. Lobar pneumonia. Chronic tuberculosis of bronchial nodes. Miliary tuberculosis of lungs, liver, spleen, and peritoneum. Caseation of one adrenal. Syphilis of myocardium and of fetal chorion.

31. CASE B.—Age, forty-two years. Gonorrhea at twenty years of age. Denied syphilis. Wassermann negative. Drinker. Clinical diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Syphilis of heart, aorta, and testes.

32. CASE W.—Age, seventy-eight years. No history of syphilis. Wassermann positive. No clinical diagnosis.

Pathological Diagnosis. Syphilis of heart, aorta, pancreas, and testes. Syphilitic peribronchitis. Chronic parenchymatous nephritis. General marasmus.

33. CASE B.—Age, forty-eight years. No history of venereal diseases. Wassermann negative. Clinical diagnosis of prostatic enlargement and uremia.

Pathological Diagnosis. Primary carcinoma of prostate. Metastases in liver. Chronic cystitis, ureteritis, and pyelonephritis. Syphilis of heart, aorta, and testes. Fatty liver and adrenals. Pulmonary edema. General atrophy. Emphysema. Infected cystotomy wound.

34. CASE A.—Age (?). No history of syphilis. No Wassermann. Clinical diagnosis of diabetes. Mitral insufficiency.

Pathological Diagnosis. Diabetes. Atrophy of pancreas. Dilatation of heart. Purulent bronchopneumonia. Subacute parenchymatous nephritis. Syphilitic orchitis.

35. CASE AR.—Age, forty-eight years. No history of syphilis. Wassermann negative. Diagnosis of diabetes. Sepsis.

Pathological Diagnosis. Diabetes. Infected squamous-cell carcinoma of finger. Ascending purulent lymphangitis of right arm. Septicemia. Syphilis of heart, aorta, pancreas, and testes.

36. CASE AL.—Age, sixty-nine years. Denied venereal disease. Wife had one miscarriage. Drinker. Wassermann not taken. Diagnosis of croupous pneumonia and pernicious anemia.

Pathological Diagnosis. Croupous pneumonia. Syphilis of heart, aorta, and testes. Syphilitic contracted kidney. Anemia gravis. General atrophy.

37. CASE MRS. BO.—Age, forty-four years. No history of syphilis. Never pregnant; no precautions taken. Wassermann negative. Died of general peritonitis.

Pathological Diagnosis. Acute purulent peritonitis. Infected laparotomy wound, posthysterectomy. Syphilis of heart and adrenals.

38. CASE W.—Age, fifty-five years. Denies venereal disease. Moderate drinker. One Wassermann test negative, second one positive. Diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Ascites. Portal stasis. Syphilis of heart, aorta, and testes. Emphysema. Chronic prostatitis.

39. CASE J.—Age, seventy-two years. Denies venereal disease. Moderate drinker. Wassermann negative. Clinical diagnosis of myocardial insufficiency.

Pathological Diagnosis. Aortic insufficiency and stenosis. Sclerosis of endocardium. Mitral stenosis and insufficiency. Cardiac hypertrophy and dilatation. Syphilis of heart, aorta, pancreas, and testes. Syphilitic ulcer of leg. Emphysema. Brown induration of lung with multiple infarcts. Early interstitial nephritis. Early stage of alcoholic cirrhosis. General atrophy.

40. CASE C.—Age, fifty-nine years. Denied venereal disease. No Wassermann. Clinical diagnosis arthritis deformans of spine. Terminal pneumonia. Pyelonephritis.

Pathological Diagnosis. Primary scirrhous adenocarcinoma of prostate with metastases in vertebræ, ribs, pelvic bones, lungs, liver, and retroperitoneal lymph nodes. Aspiration purulent bronchopneumonia with abscesses of lung. Multiple abscesses in kidneys. Chronic cystitis. Syphilis of heart, aorta, adrenals, and testes.

41. CASE CA.—Age, forty-five years. Denied venereal disease. One Wassermann test negative; second one positive.

Pathological Diagnosis. Croupous pneumonia. Chronic ulcerative colitis with multiple polyp formation. Chronic dysentery. Amyloid spleen. Syphilis of heart.

It will be seen from the above list that there are 11 cases with clinical diagnosis of recognized and treated syphilis regarded clinically as cured, 5 cases of active syphilis under treatment for symptoms of the disease, and 25 cases in which a diagnosis of syphilitic infection was excluded clinically because of absence of symptoms and denial of previous infection. It is very probable that some, if not the majority, of the patients in this third group were actually in total ignorance of any specific infection. In the case of the women it is practically certain that this was the case. There can be no doubt that many people acquire syphilis without recognizing any of the earlier stages, either through ignorance of these or because the early symptoms are slight or entirely absent. Some of the male patients in this group no doubt had had the primary sore so long before that they had either forgotten it or no longer attached any importance to it. Having long ago accepted that condition as cured, they consider it as past history and deny that it ever took place. It is, of course, a very common experience in dealing with patients of this type to receive repeated denials of the occurrence of syphilitic infection, and the information of such an infection must be drawn out by special and prolonged tactics of questioning. It is also possible that a number of these cases were congenital infections, and unrecognized by the patients. Particularly in the case of women may congenital syphilis run an unrecognized latent course throughout the patient's lifetime.

In all of these 41 patients the lesions of active syphilis were practically of the same nature, whether in cases that had been treated, or were being actively treated, or had received no treatment at all. Active syphilitic lesions were found in the heart in 36 cases, in the aorta in 32, in the testes in 31, in the liver in 4, in the adrenals in 6, in the spleen in 1 case, pancreas in 6 cases, and central nervous system in 5 cases. As five of the patients were women, and deducting these, the lesions in the testes occur as frequently as those in the heart. The organs most frequently the seat of active lesions in order of frequency of occurrence would be aorta, heart, testes, adrenals, pancreas, central nervous system, liver, and spleen. It is also of great interest to note that in these cases there were 16 cases of subacute or chronic parenchymatous nephritis; 2 of acute parenchymatous and 5 cases of interstitial nephritis, although no relationship between the syphilis and the kidney lesions can be positively affirmed. It is very probable that the central nervous system would show a much greater rate of involvement had this been regularly examined, but in the majority of these cases an examination of cord and brain was not permitted. In all five of the active cases of Class II the central nervous system was examined and showed marked syphilitic lesions.

In the determination of the existence of syphilitic infection in any given case coming to autopsy the heart, aorta, and testis in the male are the organs that should receive the most thorough examination. If the latent syphilis is present, active lesions will be found in one or the other of these organs if they occur anywhere within the body. The triad of interstitial myocarditis, aortitis, and orchitis fibrosa may be taken as a pathological complex indicating the occurrence of a syphilitic infection in the male. In medicolegal work these three organs should be chosen in preference to all others for microscopic examination when the question of syphilis is concerned. In the case of the female, the heart and aorta, pancreas and adrenals should be examined for evidences of latent syphilis, and the lesions in these organs are, as a rule, less marked than in the male body.

The number of spirochetes in old latent syphilis is usually small; only in a few cases have they been found in numbers at all approaching those of early congenital or acquired syphilis. They lie in small groups or colonies in small perivascular infiltrations; usually outside of the walls of small veins. This is particularly true in the case of the aorta, where the organisms are never found in the intimal side of the vessel, but are found colonized in the outer portion of the media, or, most frequently of all, in the adventitia around the veins of the vasa vasorum. In the heart muscle they are found in small areas of connective-tissue proliferation and infiltration around the smallest branches of the coronary vessels, particularly the veins, and in similar areas in the muscle. The amount of inflammatory infiltration may be very slight. The pancreas in every case of latent syphilis shows more or less pronounced increase of stroma, areas of intralobular pancreatitis, atrophy, and perivascular infiltrations. The syphilitic nature of all these changes has not yet been determined. Only in one of the diabetic cases have spirochetes been demonstrated in the pancreatic lesions. It is of interest to state here that six autopsy cases of diabetes occurring in our service since 1907 have all shown histological changes of syphilis, and in four of these cases spirochetes have been demonstrated in the myocardium. The adrenal lesions consist of mononuclear infiltrations in the medullary portion or at the boundary between cortex and medulla, around the veins, and also thickening of the corpuscle. Spirochetes have been demonstrated in the infiltrated areas. The lesions of the testes consist of vacuolation and disappearance of the germinal cells, hyaline thickening of the basement membrane of the tubules with gradual obliteration of the seminiferous tubules, the so-called orchitis fibrosa syphilitica chronica. A state of fibroblastic proliferation precedes the hyaline change, and spirochetes are found in the basement membrane in this early state. Small collections of mononuclear cells may be found between the tubules in the neighborhood of small vessels. Spirochetes may be found in these areas also. The close relationship of the spirochete to the seminiferous tubules makes the entrance of the organism into the tubule a very probable occurrence, and can be taken as a very strong argument for the possibility of seminal infection. In congenital syphilis and in early acquired syphilis I have found the testes swarming with spirochetes even when no histological changes can be recognized in the organ. In such cases great numbers of spirochetes must gain entrance to the tubules and pass out with the semen. The difficulties in proving this are, of course, very obvious.

I have taken as a criterion for diagnosis only morphologically typical spirochetes, and have based my findings only upon the demonstration of those showing characteristic quality and morphology. In addition to typical organisms, we find in the old latent cases especially irregular and atypical forms (beaded forms, straight forms, fragmented forms, thicker or thinner spirals, etc.) in the colonies with the typical forms. I believe these to be involution forms, but am not yet prepared to make positive statements concerning this point. This point is now being investigated. The beaded and fragmented forms may in part be postmortem changes, since they can be produced in spirochetes in syphilitic tissues left in the cold or warm room for some hours after removal from the body before the formol-fixation. Experiments with liver, spleen, and lungs of congenital syphilis containing innumerable spirochetes show that similar changes in the spirochetes can be produced by the conditions mentioned above. Taking the typical spirochetes as our criterion, there can be no question of any confusion with fibrillæ of reticulum, elastic tissue, etc. The latter, even when heavily precipitated with silver, never resemble the spirochete in morphology or quality to such an extent as to make confusion of identity possible.

Our autopsy material comes almost wholly from the University Hospital, a State hospital whose patients represent the average middle-class population of the State. It is important to note the prominent incidence of latent syphilis in this class, about one-third of the adult autopsies. Still more important is the fact, already mentioned, that the greater part of these latent cases give no clinical history of syphilis, and are in ignorance that they have acquired the disease. They entered the hospital for other conditions, most prominent of which are cardiovascular-renal symptoms and conditions. Only the autopsy reveals that they are spirochete carriers and have a latent infection of very low virulence, which in all of the cases must be very old, and not recent, because of the fibroid character of the lesions. Most of the lesions found represent healed syphilitic areas; but in all cases active areas of inflammation are still present, and can always be found after a search more or less prolonged, as the case may be. The same histological changes, often of the same degree and extent, occur in the heart, aorta, pancreas, and testes of all cases of syphilis, treated, "cured," untreated, and unsuspected.

The sociological importance of this is very great. It places latent syphilis upon a plane of importance nearly, if not equalling, that of tuberculosis, as a factor opposed to the health and progress of the race. Latent syphilis, I believe, will be found to be the chief factor in the production of myocardial insufficiency and the cardiovascular-renal complex, apparently so rapidly increasing.

My pathological experience makes me believe that the heart and aorta of every latent syphilitic are involved in the infection. From the stand-point of life insurance, latent syphilis becomes a medical and sociological factor of the greatest importance. The spirochete carrier is a bad risk. He is also a possible source of danger through infection to those with whom he lives in most intimate contact. In these old latent cases seminal transmission is probably the most dangerous possibility to be considered.

The question of a possible reinfection has been suggested in explanation of some of these cases. No clinical evidence, of a second infection, of course, exists in any one of these cases; and in most there is no history of the first infection. I think such a possibility very improbable. I, myself, have never seen a true reinfection, and regard the relatively few cases described in the literature as not above suspicion. Sores in all respects resembling the hard chancre may appear upon the genitals or other portions of the body in late active and treated cases of syphilis. Even on microscopic examination they cannot be distinguished from the primary chancre. A primary sore may also be made to disappear early by the use of preventive or curative mercurial ointments or by one or two injections of salvarsan; but it may return after a few weeks or months. I have seen several cases in which such a recurrence of the chancre took place six months after the primary sore had disappeared under such treatment, and without chance for reinfection. In one case recurrence took place one year later. Had opportunities for reinfection been present, such recurrent primaries might easily be regarded wrongly as reinfections.

I believe that many of these latent cases without history are innocent congenital cases or are the victims of familial infection. Congenital syphilis, in the female, and in the third generation has an especial tendency to run a mild latent course, sometimes without any clinical sign or symptom. It may not be recognizable at all during life. The same thing is sometimes true of certain familial infections; certain members of the infected family may show absolutely no clinical signs or symptoms, except perhaps a positive Wassermann. This may also be negative. In other cases obscure signs of the disease (ocular alone) may be the only evidence found of the infection. The sociological and medical problems associated with congenital syphilis are very great, and we are just beginning to appreciate them.

As to the Wassermann reaction in latent syphilis a certain percentage of cases will give a positive reaction, but many will be found to have a negative reaction. Blood and spinal fluid will often give contradictory results. Under given conditions only strongly positive reactions have any positive diagnostic value; the negative Wassermann cannot be taken as any evidence of the absence of latent syphilis.

The apparent symbiosis of spirochetes within such organs as the heart, aorta, and testes through a period of many years without causing greater damage or giving rise to more marked symptoms must be taken as proof that the organisms have a very low virulence in such cases. "Cured" syphilis in many cases, if not all, is but a latent infection or "symbiosis," with spirochetes that have a very low virulence, in some cases not much greater than that of the intestinal flora. It becomes increasingly important to know the conditions under which organisms remaining so relatively inactive over long periods of time may at times renew their aggressiveness and cause more marked damage.

The general hygiene of the spirochete carrier is probably of as great importance as the general hygiene of latent tuberculosis. This is a point not yet sufficiently emphasized in the treatment of syphilis.

The therapeutic lesson is evident. Promises of cure within definite time-limits can never be safely made, and our advice as to treatment must include the possibility of treatment extended over many years. The syphilitic must be treated as a germ carrier. The latency of the infection seems to be the same in many untreated cases as in those receiving very good treatment. Our present-day treatment seems only to succeed in rendering the infection latent rather than in curing it. Clinical cures may not be cures at all, as shown by the autopsy. From the stand-point of eugenics it may also be said that absence of symptoms, or even of history of infection, and negative Wassermann reaction cannot be taken as an absolute criterion of freedom from latent syphilis.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Edited by George Morris Piersol, M.D. Monthly. Illustrated. 1920 pages yearly. Price, $5.00 per annum.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, founded in 1820, has long been recognized as the leading medical journal of the English-speaking race. From the first it sought the epoch-making papers, and becoming recognized as their medium, it has, in turn, been sought by those who have had discoveries or real advances in the art and science of medicine to announce in its Department of Original Articles. During 1916 *The American Journal* will still further develop a feature that has proved most useful and popular, namely, a series of Special Articles, written by prearrangement with men of the highest authority, and covering present-day topics of the greatest importance and interest. These articles are designed to be clinical and practical, and to present important advances and the latest knowledge clearly and concisely, with particular reference to application in daily work. The Department of Book Reviews will continue to comprise critical and discriminating estimates of important new books, as well as briefer notices of books of less importance and of new editions. The Department of Progress of Medical Science, under the charge of recognized specialists, will continue to summarize the actual advances in the art and science of medicine appearing in the leading medical periodicals of the world.

PROGRESSIVE MEDICINE

A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES, COVERING THE ENTIRE DOMAIN OF MEDICINE. Edited by Hobart Amory Hare, M.D., Professor of Therapeutics in Jefferson Medical College, Philadelphia; Physician to the Jefferson Medical College Hospital, etc. Assisted by Leighton F. Appleman, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. In four octavo volumes, containing 1200 pages, amply illustrated. Annual subscription price, in heavy paper covers, $6.00, *net;* in cloth binding, $9.00, *net.* Carriage paid to any address.

PROGRESSIVE MEDICINE is the story of the progress, discoveries and improvements in the various branches of the medical and surgical sciences, and is published four times a year, in March, June, September and December. The matter presented is the digested essence of the entire medical literature of the world published during the previous twelve months, modified, explained and criticised in the light of the personal experience of the contributor. By this method useless information is discarded and only that which is valuable and really helpful to the practitioner is retained. Practicality and thoroughness are the controlling features. The contributors are authorities in their respective lines, and their experience in private and hospital practice enables them to choose unerringly that which their brother workers require. Every article is original, the veritable product of the author whose name it bears. The style is narrative in form, hence easy to read. The interpretation of the facts stated is given and their bearing upon the whole subject under consideration is clearly and simply indicated.

COMBINATION RATES

The American Journal of the Medical Sciences	per annum,	$5 00
Progressive Medicine (heavy paper covers)	"	6 00
Progressive Medicine (cloth binding)	"	9 00
Progressive Medicine (paper covers) and the American Journal	"	10 00

PHILADELPHIA
706-8-10 SANSOM ST

LEA & FEBIGER

NEW YORK
2 WEST 45TH ST.

University of Michigan.
Pathological Laboratory.
Contributions.

448734
Michigan, University of. Pathological Laboratory
Contributions.
v.7(1915-16)

P
Med
M

Biological
& Medical
Serials

NAME OF BORROWER.

DATE.

University of Toronto
Library

Biological
& Medical
Serials

DO NOT
REMOVE
THE
CARD
FROM
THIS
POCKET

Acme Library Card Pocket
LOWE-MARTIN CO. LIMITED